high-thoracic epidural analgesia during and after thoracic surgery

m.a.w.m. hasenbos

HIGH-THORACIC EPIDURAL ANALGESIA DURING AND AFTER THORACIC SURGERY

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HIGH-THORACIC EPIDURAL ANALGESIA DURING AND AFTER THORACIC SURGERY

PROEFSCHRIFT

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Aan de nagedachtenis van mijn moeder,
aan mijn vader,
aan Michelle.

CONTENTS

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CHAPTER 1

INTRODUCTION AND AIM OF THE STUDY

1.1 Introduction

Even under ideal circumstances, surgery and anaesthesia cause a certain unavoidable risk to the patient. Pre-existing systemic disease, trauma and the kind of operation often increase this risk. "The general availability of arterial blood gas measurements has made it apparent that respiratory failure is now the major cause of post-traumatic and post-operative death" (Peters, 1972). This applies to patients with normal lungs. It takes little imagination to predict that patients with pre-existing pulmonary disease are in a high risk group. The most important pulmonary disease is chronic obstructive pulmonary disease (COPD), which includes chronic bronchitis, emphysema and asthma. The mortality by respiratory failure alone in COPD patients has been reported to be four times higher than mortality due to all causes in non-COPD patients in a general surgical population (Tarhan, 1974). Factors such as advanced age, cardiovascular disturbances, cigarette smoking, thoracotomy and administration of opiates for pain treatment contribute to the already increased risk in COPD patients.

Thoracotomy is a very painful operation creating a great need for postoperative analgesia (Parkhouse, 1961; Katz, 1980). Many studies comparing general with regional anaesthesia for patients with normal pulmonary function, have consistently failed to demonstrate any positive correlation between technique of anaesthesia and incidence of postoperative complications (Rovenstine, 1936; Dripps, 1946; Hamilton, 1961; Egbert, 1962; Boutros, 1965), except in COPD patients (Tarhan, 1974). Regional anaesthesia reduces the incidence of postoperative thrombo-embolic complications and blood loss after hip surgery and prostatectomy, while data from other procedures with regard to postoperative morbidity are inconclusive (Kehlet, 1984).

To see the effect of the type of anaesthesia and/or analgesia on

the postoperative course several parameters as pulmonary function, alveolo-arterial oxygen difference, P_aO_2 and P_aCO_2, pain scores, stress-response and even monocyte and lymphocyte functions, can be used All of them are laboratory results, some of them are of academical interest, the final goal however is the reduction of major clinical complications as atelectasis and pneumonia. The latter two complications cause impaired gas exchange in the lungs and are directly related to the survival of a patient.

1.2 Aim of the study

The main purpose of this study is to investigate the influence of the type of analgesia during and after the operation on the incidence of postoperative pulmonary complications.

Four types of analgesia are compared for various thoracic operations, and the incidence of major complications (atelectasis and pneumonia) are investigated

The four types of analgesia are:

1 During the operation i v. nicomorphine.
After the operation i.m. nicomorphine.

2. During the operation epidural bupivacaine 0.5% + adrenaline 1 . 200,000.
After the operation epidural nicomorphine.

3. During the operation i.v nicomorphine.
After the operation epidural nicomorphine.

4. During the operation epidural bupivacaine 0.5% + adrenaline 1 . 200,000.
After the operation i.m nicomorphine.

The four groups are schematically listed in table 1, according to

their analgesia regimes during and after the operation. Groups belonging to the same column received equal analgesia treatment during surgery, groups in the same row received equal analgesia after the operation (see table 1).
If there is statistically significant difference between the groups 1-4, the best combination of analgesia during and after the operation with respect to the prevention of postoperative pulmonary complications can be selected.

Table 1: Analgesia groups.

Type of analgesia during the operation and after the operation, in the various groups (1-4). Drugs for analgesia used are nicomorphine (N.M.) and bupivacaine (Bu).

	During operation	
	i.v. N.M.	epid. Bu
Postoper. i.m. N.M.	1	4
Postoper. epid. N.M.	3	2

If the best combination of analgesia during and after the operation is found a few questions, however, remain.

- Is this way to achieve analgesia safe? This will be discussed in chapters 7 and 9.
- Is the technique satisfactory for pain relief? This also will be discussed in chapters 7 and 9.
- What are the effects of the high thoracic epidural technique with local anaesthetics on the cardiovascular system? This will be the subject of chapter 10.
- What are the consequences of the technique with regard to the respiratory system? This will be discussed in chapter 11.

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CHAPTER 2

ANATOMY

2.1 Anatomy with special reference to the thoracic epidural space

The anatomy of the epidural space will not be pointed out extensively, but only the most important characteristics with regard to the thoracic approach of the epidural space. For more detailed information the reader is referred to the excellent textbooks of Bromage (1978) and Cousins (1980).

The boundaries of the epidural space are:

Cranial: the foramen magnum where periosteal and spinal layers of dura fuse together.

Caudal: the sacrococcygeal membrane.

Frontal: the posterior longitudinal ligament covering the posterior aspect of the vertebral bodies and the intervertebral discs.

Dorsal: the anterior surface of the vertebral laminae and the ligamenta flava.

Lateral: the pedicles of the vertebrae and the intervertebral foramina.

When puncturing the epidural space, the skin, subcutaneaous layer, supraspinous ligament, interspinous ligament and the ligamentum flavum are encountered. The average distance between skin and epidural space is between four and six centimeters, when the median approach is performed at the lumbar level. At the thoracic level it varies between 3 and 8 cm depending on the level of the epidural puncture and whether the median or paramedian technique of

introducing the needle is used (see chapter 4). In the mid-thoracic region there is a steep angulation and overlap of the spinous processes and laminae, here the only technique of introducing the epidural needle is the paramedian approach (see figures 2.1 and 4.1) Above the fourth and below the eighth thoracic vertebrae the angulation gradually becomes less, and both the median and paramedian approach of introducing the epidural needle become possible (see figures 2.1 and 4.1).

At the thoracic level one is dealing with the spinal cord, which terminates at the lower border of the third lumbar vertebra in newborn infants, but ascends during growth as the spinal column lengthens, and in adolescents it ends at the lower border of the first lumbar vertebra or upper border of the second. The thinnest part of the spinal cord is at the mid-thoracic region between the cervical and lumbar enlargements. The nerve roots are correspondingly thick at the level of the cervical and lumbar enlargements and proportionately fine at the mid-thoracic level.

The width of the posterior epidural space varies, depending on the dimensions of the bony spinal canal, in relation to the size of the cord and its coverings at each level. At the second lumbar interspace the distance between the ligamentum flavum and the dura is about 5 to 6 mm at the midline, at the mid-thoracic level 3 to 5 mm in the midline and at the lower cervical region the distance narrows to 1.5-2 mm. The total epidural area increases from cranial to caudal, because the bony canal is larger caudal than cranial. This may be an important factor to explain why local anaesthetics injected at high-thoracic level spread more caudally than cranially.

The epidural space is filled with fat, lymphatic and blood vessels. The major portion of the venous blood vessels is situated in the anterolateral part of the epidural space, out of reach of a correctly placed epidural needle. Pressure changes in the thoracic and abdominal cavities are transmitted by the intervertebral foramina to the epidural veins.

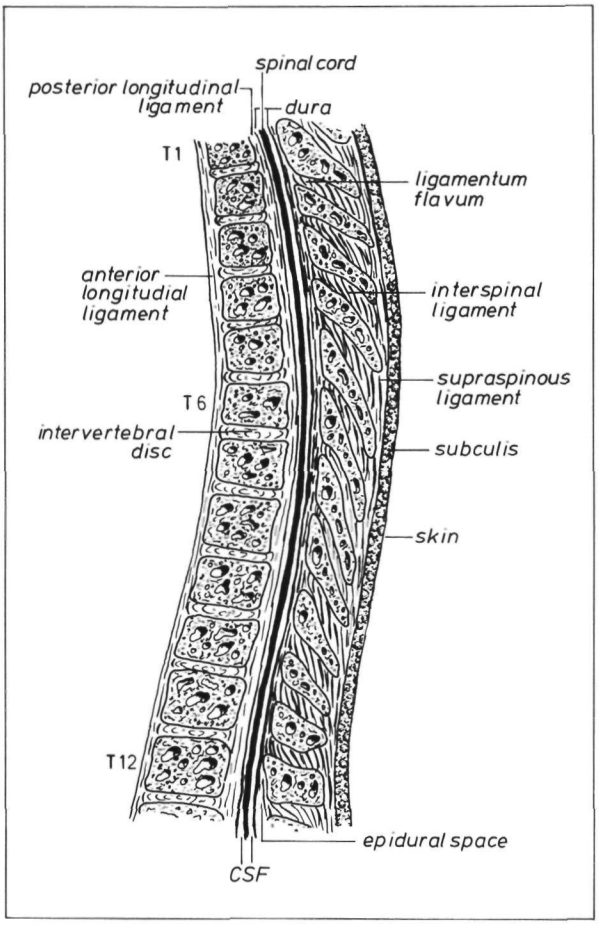

FIG. (2.1) *Median sagittal section of the vertebral column. Note the steep angulation of the spinous processes at the mid-thoracic level, and the presence of the spinal cord at the thoracic level.*

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CHAPTER 3

PHYSIOLOGY

3.1 Action of local anaesthetics and opiates on the nervous system

Painful stimuli are transmitted through slow conducting A-δ and C fibres. The afferent nerves enter the dorsal horn of the spinal cord and terminate in the Rexed's laminae where contacts with other pathways are made. The epidural effects of opiates are believed to result mainly from an action on the neuronal transmission in the dorsal horn of the spinal cord. This results in long lasting and segmental analgesia, without sympathetic and motor blockade (Nordberg, 1984).

This is in contrast to epidural analgesia by local anaesthetics, which can produce sympathetic blockade, sensory blockade and more or less motor blockade. When all these three modalities are blocked this results in epidural anaesthesia. If there is a blockade of only one modality (e.g. sensory blockade) or if all three modalities are blocked depends on the dosage and potency of the local anaesthetic and whether or not adrenaline is added. The most important action of local anaesthetics is on the spinal roots. Other possible sites of action are the paravertebral nerves and the spinal cord (Bromage, 1978 chapter 4).

From the various systems affected by epidural administration of local anaesthetics, only the cardiovascular and respiratory systems are discussed (as have been reviewed by Bromage, 1978, chapter 10) with regard to the changes that may occur during thoracic epidural analgesia.

3.2 Cardiovascular system

According to Bromage (1978) epidural analgesia with local anaesthetics may influence the cardiovascular dynamics as classified in the following scheme:

Neural effects:

1. These effects are due to segmental sympathetic efferent blockade which results in dilatation of resistance and capacitance vessels. This causes an afterload reduction and reduces the cardiac work, but may also reduce the cardiac output by reduction of the venous return.

2. The paralysis of cardiac sympathetic fibers from the upper four or five thoracic segments, results in loss of chronotropic and inotropic drive to the myocardium, leading to bradycardia and reduction of ejection force (see figure 3.1).

Pharmacological effects:

1. These effects are due to vascular absorption of local anaesthetic from the epidural space, leading to significant concentrations of local anaesthetic in the circulation and consequent distant effects on smooth muscle and β-receptors. These effects are relaxation of the smooth muscle and a fall in cardiac output from β-receptor blockade. These depressant effects of local anaesthetics are dose and pH dependent and are most severe in the presence of acidosis.

2. The influence on cardiovascular dynamics may also result from β-receptor stimulation as a result of vascular absorption of adrenaline, if this is present in the epidural solution, leading to a rise in cardiac output and a fall in peripheral resistance. The result may be difficult to interpret, unless one realizes that the process of blockade is not an absolute event.

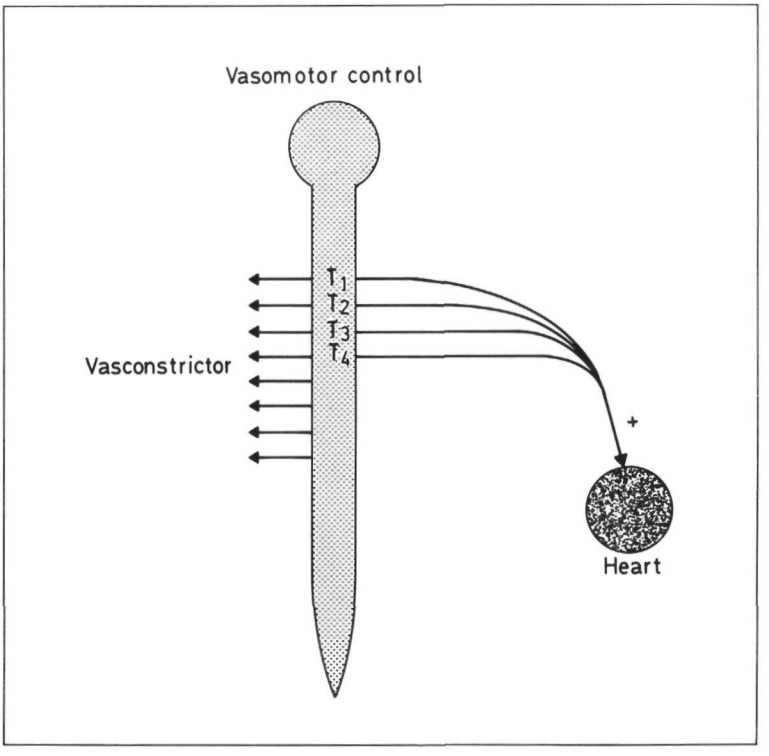

FIG. (3.1) *Segmental and cardiac distribution of the sympathetic outflow.*

The effect of partial paralysis of cardiac sympathetic fibers from the upper four thoracic segments, was most precisely studied by Otton and Wilson in 1966. This study was not complicated by tachyphylaxis or by high levels of circulating local anaesthetics. In order to isolate and identify the extent of cardiocirculatory changes following epidural analgesia, six fit awake preoperative patients were studied in the control state and after upper thoracic block. Cardiocirculatory dynamics were assessed by measuring arterial and central venous pressures, heart rate, cardiac output (indocyanine dilution) and by calculating local systemic vascular resistance and left ventricular work. Following epidural blockade by mepivacaine 1%, (1 mg/kg body weight approximately) at the C7-T1

interspace, there was a significant reduction in cardiac index (16%) and in heart rate, whereas the stroke volume remained constant in spite of a significant rise in central venous pressure (1.9 cm H_2O). A decline in arterial pressure (7%) parallelled the reduction in minute flow.

So upper thoracic epidural analgesia reduces cardiac performance in two ways; by slowing the heart rate and by reducing the myocardial response to its filling pressure. However, the intensity of these effects depends on the type of local anaesthetic, its dosage and whether or not adrenaline is added (Sheskey, 1982).

3.3 Respiratory system

According to Bromage (1978) respiratory motor neurons, in common with all other motor cells, require afferent input to perform their normal functions. Similar dependence exists for the phrenic reflex (figure 3.2).
One would expect, that deafferentiation by epidural blockade up to the level of T1, blocking the sympathetic nervous system, results in unopposed parasympathetic activity. Since one assumes a predominance of the vagal constrictor pathways to the airways, this could result in bronchoconstriction and subsequent impaired gas exchange in the lungs, especially in patients with bronchial hyperreactivity. However, in clinical studies (Hennek, 1984, Hasenbos, 1985), using high-thoracic epidural block, this has not been reported. The reason for this contradiction is, that by deafferentiation the reflex apparatus becomes tractable. Depending on the local anaesthetic used (no motor blockade), an unhindered repiration develops, free of the expiratory effort seen under light anaesthesia or upon surgical stimulation.

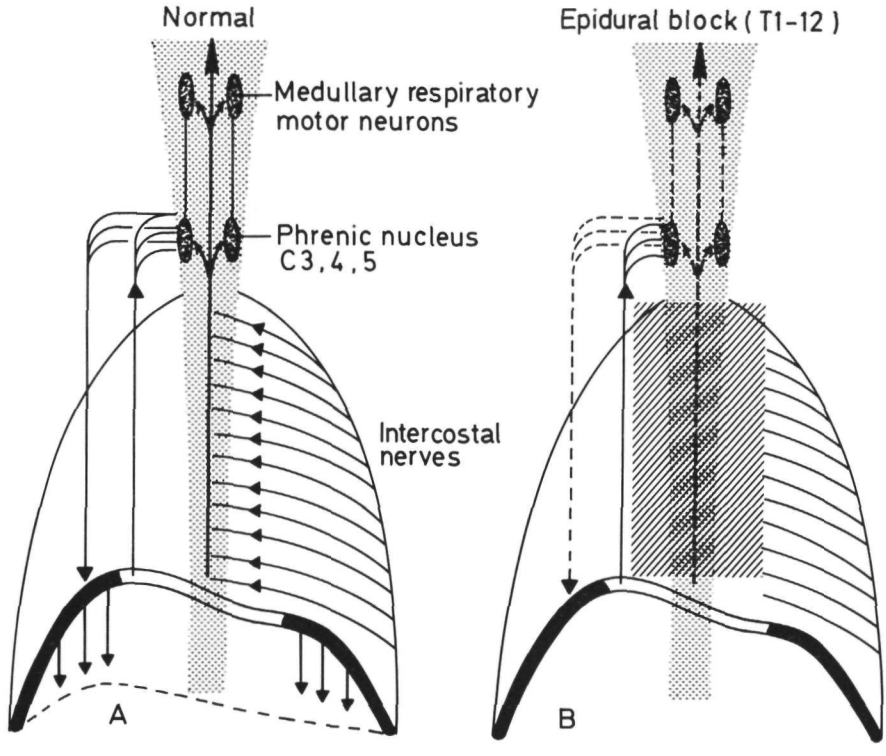

FIG. (3.2) *Attenuation of respiratory reflexes by reduction of collateral sensory input.*

A. Normal motor response of diaphragm to stimulation of central portion, under light anaesthesia. Phrenic and medullary respiratory motor neurons are facilitated by sensory input from caudad sources in the chest wall and elesewhere.

B. Abolition of facilitatory afferent input by epidural blockade to T1. Failure of diaphragmatic response to direct stimulation. (According to and with permission of Bromage, 1978, and the publisher).

Two other factors that may play a role in initiating bronchial relaxation besides deafferentiation are:

1. Changes in the character of lung surfactant which leads to a decrease in surface tension of alveolar lining and a rise in compliance of the lung.
2. Lowered arterial and venous tone from sympathetic blockade tends to relieve any pre-existing pulmonary congestion (Bromage, 1954).

One could expect that denervation of the thorax by high epidural blockade, using local anaesthetics, changes the posture of the rib cage by motor blockade. Measurements of functional residual capacity under tranquil conditions by McCarthy in 1976 did not confirm this, although segmental blockade extended between the second and third thoracic segment and the upper lumbar segments.

So thoracic epidural blockade has the following advantages with respect to ventilation:

1. Due to neural blockade the respiration type is free of expiratory grunting that usually accompanies light anaesthesia or surgical stimulation.

2. Controlled ventilation can be performed without the need for muscle relaxants.

3. Anaesthesia can be very light, so after the operation the patient can cooperate at once with physiotherapy with less pain.

4. In COPD patients it may prevent and even cure bronchospasm (Bromage, 1978, chapter 13).

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CHAPTER 4

PUNCTURE OF THE THORACIC EPIDURAL SPACE

4.1 Introduction

The technique of localization of the thoracic epidural space is different from the technique for localization of the lumbar epidural space. Knowledge of the anatomy at this level is necessary for a safe and a good puncture of the thoracic epidural space (see figure 4.1).

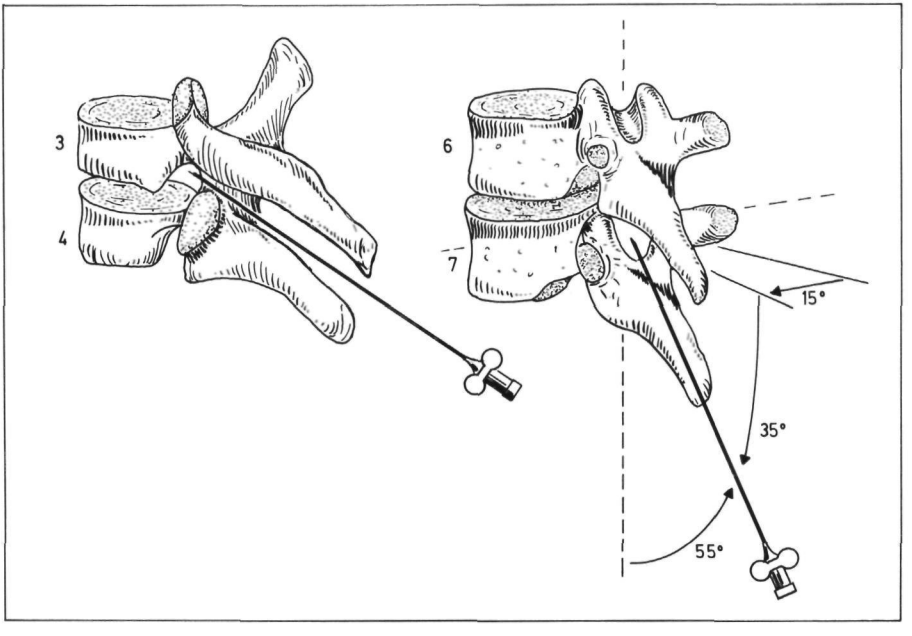

FIG. (4.1) *Thoracic epidural approach at the T6-T7 level. Note extreme upward angulation of the needle required in the mid-thoracic region, also with the paramedian approach. If one inserts the needle at T3-T4 level both paramedian and median approach can be performed.*

Spinous process:

- At the T6-T7 level there is an extreme downward slope of the spinous process so that the inferior border is opposite to the mid-point of the lamina below.
  At the T3-T4 level the downward slope is less steep, and the inferior border is higher than the mid-point of the lamina below, but still on that lamina.
  As a consequence of the extreme downward slope of the spinous processes at the T6-T7 level, only the paramedian approach for puncturing the epidural space is possible. At the T3-T4 level both the paramedian and median approach can be performed (see figuur 4.1).
- The processes are very close together and have a small posterior surface. As a consequence the identification is difficult.

Interspinous ligament:

- This ligament is difficult to identify because the spinous processes are close to each other.

Lamina:

- These are broader but are shorter in vertical dimension, so a large surface for identification is available.

Ligamentum flavum:

- At the thoracic level it is less thick than mid-lumbar.

The thoracic epidural space:

- The depth of the thoracic epidural space is 3-5 mm in the mid-line, which is less than in the lumbar region but more than in the cervical region. Laterally the epidural space narrows (see figure 4.2).

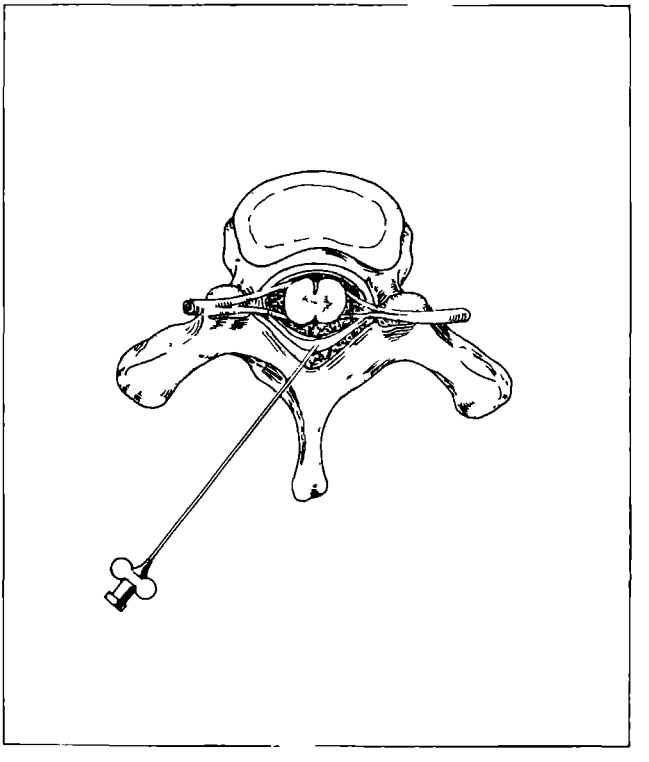

FIG. (4.2) *Cross sectional view of the spinal canal. The widest part and safest point of entry into the epidural space is in the mid-line. The lateral portion of the epidural space is narrower and the epidural veins are most prominent there.*

4.2 Technique of the thoracic epidural puncture

The description of the paramedian approach will be given, however, the median approach is possible as well at the T3-T4 level.

1. The patient is in the sitting position, his back and neck well flexed. The legs of the patient are over the side of the bed or the operating table, his feet on a stool, and his arms folded across his chest. An assistant stands in front of the

patient and supports the patient's shoulders.

2. The back of the patient is disinfected by iodine. A skin weal with lidocaine 1% is made. Further infiltration with lidocaine 1% is performed by inserting the (50 mm x 0.8 mm) needle 1 to 1.5 cm lateral to the caudal tip of the spinous process, corresponding to the intended level of needle insertion. The long needle infiltrates from the skin down to the lamina: first perpendicular to the skin to reach the lamina and second by walking over the lamina in the mid-line direction, until contact is lost. Then the needle is withdrawn.

3. With a scalped blade a small skin incision is made.

4. A 16 G Tuohy needle with wings is used. Both hands, resting against patient's back, assure a firm grip and excellent control of the needle, which is necessary for the hanging drop technique. When the tip of the Tuohy needle reaches the lamina, the needle is directed upward (about 55 degrees to the long axis) and inward (about 10 to 15 degrees) over the lamina, with the tip of the needle in the median direction. When the needle slides off the cranial edge of the lamina, the ligamentum flavum is entered (see figure 4.1)

5. The stylet is now removed.

6. A drop of fluid is placed in the hub of the Tuohy needle.

7. The Tuohy needle is now advanced very carefully, mm by mm, synchronously with patient's inspiratory movements to profit from any slight increment of negative pressure. When the epidural space has been entered, the fluid disappears from the hub as if it is sucked away. Another drop of fluid is placed in the hub of the needle, and if the drop is sucked away again this confirms the position of the needle in the epidural space.

8. The epidural catheter is inserted through the needle and directed cephalad 3-4 cm. No resistance will be met. This distance is sufficient for the catheter to remain in place during normal activity. The paramedian approach confers a very slanting direction to the epidural needle so the orifice of the Tuohy needle tip is directed along the axis of the canal and this facilitates subsequent passage of the epidural catheter. If the patient complains of pain, advancement of the catheter should be stopped and the needle with catheter withdrawn. The pain may be caused by pressure of the catheter on a nerve root or the cord itself, and pushing the catheter onward may cause injuries to the above mentioned structures.

9. Once the catheter is in place, the needle is withdrawn over the catheter taking care that the catheter remains in position. An aspiration test is done to exclude that the catheter has entered a blood vessel or the subarachnoid space, and 1 ml of saline is injected to ensure the catheter is open and not kinked.

10. The port of entry of the catheter in the skin is covered with sterile gauze. The catheter is fixed against the skin on the patient's back. The catheter is taken over the patient's shoulder and fixed on the chest.

11. A bacterial filter is connected and a test dose of local anaesthetic usually 3 ml lidocaine 2% is given, and the effect after 10-15 minutes evaluated before the therapeutic dose is administered.

4.3 Discussion of the technique used

Ad.1: the sitting position.

The sitting position is preferable for several reasons:

- The spinous processes are more clearly visible and better palpable because the soft surface of the bed does not affect the spinal curvature.
- For COPD patients, especially it is more comfortable to sit upright.
- Particularly in obese patients the mid-line is more easily identified.

As a consequence of the sitting position, the premedication has to be light.

Ad.2: Paramedian or median approach.

The paramedian has some advantages in comparison to the median approach:

- The lamina of the vertebral arch forms a long landmark and enables the depth of the ligamentum flavum from the skin to be measured, thereby providing a point of orientation.
- The paramedian approach is possible at every level of the thoracic vertebral column.
- The supra spinous and inter spinous ligaments are not penetrated by the Tuohy needle. Trauma to these ligaments has been suggested as a cause of local backache, especially in older patients in whom these ligaments are frequently calcified.

Ad.4: Needle with wings.

At high-thoracic level a Tuohy needle with wings has to be used. These wings give the anaesthetist a firm grip on the needle with excellent control, necessary for the hanging drop technique.

Ad.7: The negative epidural pressure.

For identification of the thoracic epidural space, a technique for localization is used, which supposes a negative pressure in the epidural space at this level.

There are two mechanisms for the origin of this negative pressure:

- Transmission of the intermittant negative pressure of the thorax to the epidural space (Bromage, 1978, chapter 5). This mechanism is favoured by the sitting position.
- Bulging of the ligamentum flavum in advance of the needle with its rapid return to the resting point once penetrated (Zarzur, 1984).

The first mechanism is always present in the high-thoracic epidural space, the second mechanism is not, which may have possible causes:

- Insufficient flexion of the spine which would result in the ligaments flavum being "slack" so that the degree of bulging would be slight.
- The needle could have passed exactly between fibers in the ligamentum flavum, when these fibres are scanty.
- The ligament might have been perforated in its lower border adjacent to its insertion into the vertebral lamina which would hamper its ability to bulge.
- The lumen of the needle might have been obstructed after withdrawal of the stylet.

Ad.8: Level of puncture and catheter used.

To block the sensory inervation of the chest wall, the normal motor response to direct stimulation of the diaphragm and most of the afferent input from the lungs and airways, the level of analgesia has to extend from T1 to T10-T11. The reason for injecting at T3-T4 and not at T6-T7, is the preferential spread of local anaesthetic solution downwards. This may be due to the

increased volume of the epidural space from cranial to caudal.

Excessive advancement of the catheter causes complications, the catheter can curl-up and sometimes pass outward through an intervertebral foramen into the paraspinal space (Bridenbaugh, 1968). During advancement of the catheter, the conscious patient may complain of paresthesia as the tip slides past the dural-covered nerve roots.

In the beginning of the present study the epidural catheters used were from Arrom/Racz; they are of a flexible guide wire type and cannot kink. Non-kinking of the epidural catheter is especially important in thoracic surgery, since the patient must cooperate in physiotherapy. Another advantage of this type of epidural catheter is the fact that it is clearly visible on X-ray, so the exact position of the catheter is known.
Reasons to abandon this epidural catheter are almost the same as Riegler (1984) describes in his paper:

- Catheter leakage either at the skin interface or just below the injection port particular after prolonged usage.
- The difficult or impossible injection if the catheter injection port is screwed on too tight.
- The high costs of the catheter.

Because of the many complaints the factory has now developed a new epidural catheter (Arrow catheter), which has all the advantages described. The only disadvantage is the price. The catheter used now is the Perifix (Braun Company). This catheter theoretically may kink, but in practice this is never encountered. However, the catheter is not visible on X-ray, but the price is relatively low.

4.4 References

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CHAPTER 5

SPECIFIC SIDE EFFECTS AND COMPLICATIONS OF THORACIC EPIDURAL ANALGESIA

Since most of the general side effects and complications of epidural analgesia have been described in the various textbooks, these subjects will not be discussed here. In the setting of this thesis, concerning high-thoracic epidural analgesia, only two complications which can occur with this technique will be discussed.

5.1 Spinal cord damage

In performing thoracic epidural block one of the most feared complications is damage to the spinal cord (see figure 2.1). Epidural puncture at this level therefore should only be performed by the highly skilled anesthesiologist (Bromage, 1978). Trauma to dorsal roots by a needle or an epidural catheter is accompanied by pain. Any complaint of pain during induction or insertion of the catheter should be taken as an urgent signal to stop and wait until the patient can be questioned about the nature of the pain. Never persist in injecting solution or advancing a needle or catheter if the patient complains of pain or shows any sign of discomfort. With the patient asleep under general anaesthesia, this warning sign is removed, and therefore it is required to induce blockade only in the conscious patient. Because thoracic epidural block is not performed as frequently as lumbar epidural blockade, it is difficult to estimate exactly the incidence of direct trauma to the cord after performing thoracic epidural block. The consequences for the patient after spinal cord damage may be disastrous. Great gentleness, precision and manual control are the basic essentials for success and to avoid trauma and complications. From the few case reports (Bromage, 1978, chapter 14), the following recommendations can be given:

- The hanging drop technique should be first choice at the thoracic level, because a sticky syringe may be the reason for damage to the cord while performing the loss of resistance test.
- Complaints of stabbing pain are imperative calls to stop, and to try elsewhere or to change the anaesthetic technique.
- Care must be taken to prevent plugs in the needle, because sometimes no cerebrospinal fluid can be aspirated, while the needle proves to be in the subarachnoid space.

5.2 Late respiratory depression

In 1979 Behar first reported the effective use of epidural opiates in humans. A multitude of clinical applications followed. Systematic study of epidural opiates began with a brief report of pharmacokinetics of meperidine following epidural administration with simultaneous study of change in neurologic function (Cousins, 1979). This initial study provided evidence that opiates epidurally applied reached the spinal fluid very rapidly and that analgesia could be obtained in the absence of "analgesic" blood concentrations. Since other neurologic functions, including sympathetic vasoconstrictor responses, were intact, the term "selective spinal analgesia" was suggested (Cousins, 1979).

The serious complication of delayed respiratory depression was reported soon after clinical use of epidural opiates in humans (Glynn, 1979, Liolos, 1979) and stimulated appropriate studies of this and other effects of epidural opiates in man (Nijhuis, 1980). For epidural injection of opiates a model can be proposed which, however, is not a definite model because key data are currently lacking.
The following factors should be taken into account:

1. Hydrophilic opiates such as morphine versus more lipophilic opiates such as nicomorphine. The partition coefficients at pH 7.40 of morphine and nicomorphine are 1.42 and 30.15

respectively (Dirksen, 1983).

2. The degree of ionization in the various compartments (spinal cord, CSF, epidural space) as a function of the local pH.

Ad.1. What happens after administration of a lipohpilic drug as nicomorphine in the epidural space? Because of its lipophilicity the drug will be tranferred rapidly into spinal radicular arteries and veins and pass the dural membrane to enter the CSF. Also due to its lipophilicity not much nicomorphine will remain in the CSF (in contrast to morphine) to be carried cranially and give rise to a potential respiratory depression, but the drug will wander to the spinal cord's opiate receptors. However, the venous vascular absorption will be responsible for a relatively rapid (in comparison to morphine) release from these receptors, depending on the affinity for the opiate receptors. So analgesia by nicomorphine will be rapid of onset and intermediate in duration.

On the contrary morphine, being much more hydrophilic, will transfer much more slowly across membranes, but its concentration will reach higher levels in the CSF. This implies a higher risk for respiratory depression. This correlates well with its clinical effects of delayed onset and prolonged duration of action (Nordberg, 1984).

Ad.2. In the CSF the pH is lower than in the epidural space. In this environment morphine shows a more marked increase in ionization than nicomorphine, which also attributes to the risk of respiratory depression (Dirksen, 1983).

Despite its wide application at thoracic epidural level, in elderly patients and in patients with impaired respiratory function, no respiratory depression has been reported following the epidural administration of nicomorphine (Pinckaers, 1982; Dirksen, 1984; Hasenbos, 1985). All three factors are known to normally increase the risk of respiratory depression (Gustafsson, 1982). A number of clinical reports of respiratory depression have been published after epidural administration of morphine (Gustafsson, 1982; Cousins, 1984).

If analgesia with opiates by high-thoracic epidural technique is applied, several recommendations can be given:

- Use lipophilic opiates.
- Do not give additional parenteral opiates.
- Be aware that CNS-depressant drugs may potentiate the effects of opiates.
- The dosage chosen must be in concordance with patient's age, physical condition and kind of operation performed.

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CHAPTER 6

POSTOPERATIVE COMPLICATIONS AFTER THORACIC SURGERY

6.1 Incidence of postoperative pulmonary complications

The incidence of postoperative pulmonary complications varies very much from one study to another. The number of complications is related to the kind of operation performed, the age and ASA class (classification according to the American Society of Anesthesiologists) of the patient, the number of COPD patients in the populations studied, whether or not a study is pro- or retrospective and depends on the definition of a pulmonary complication. In prospective studies the incidence of pulmonary complications will be higher because patients are systematically examined, this in contrast to retrospective studies based on complications registered in the patient records. Also the definitions of a pulmonary complication varies from postoperative cough with fever, to more objective signs as atelectasis based on chest X-rays.

Most authors agree that the incidence of pulmonary postoperative complications is highest in patients undergoing thoracotomy (Kaplan, 1983, part V). The pulmonary complications can be divided in infectious and non-infectious categories. The infectious category is mainly represented by postoperative pneumonia, the non-infectious category mainly by atelectasis. Since atelectasis is the most significant cause of postoperative morbidity (Kaplan, 1983, part V), infectious complications will not be discussed.

Atelectasis is often subdivided into macro-atelectasis (loss of lung volume on X-ray) and micro-atelectasis (not visible on X-ray, but manifested by cough, fever or widened alveolar-arterial oxygen pressure gradient). Both forms of atelectasis contribute to postoperative hypoxemia and may cause hypercapnia and respiratory insufficiency. Factors known to increase the risk of postoperative

pulmonary complications include pulmonary disease, abnormal pulmonary function, cigarette smoking, aging, obesity, upper abdominal or thoracic surgery and prolonged anaesthesia time (Harman, 1979). As mentioned before, atelectasis is the most significant cause of postoperative morbidity and the incidence sometimes reaches 100 percent of patients undergoing thoracotomy for pulmonary resection (Kaplan, 1983, part V). Other authors (Harman, 1979; Tisi, 1979) do not specify for atelectasis in the number of pulmonary complications.

Since most thoracotomies take place in elderly patients with bronchial carcinoma, this group is of particular interest. A study of 8781 patients with bronchial carcinoma who were operated by seven surgeons in England during the years 1949-1980, showed that during this period operative mortality had been diminished (Belcher, 1983). The mortality from lobectomy had changed slightly (7%), but the death rate from pneumonectomy had diminished from 13% during the first six years to 7% in the last five years. These mortality figures are in accordance with figures presented by other centres in the UK and the USA (Belcher, 1983). Breyer (1981) reported 218 thoracotomies over a ten years period for patients older than 70 years. The operative mortality of 5% for both pneumonectomy and lobectomy patients compares favourably with that reported by other centres. He concluded that a patient should not be denied thoracotomy because of age.

6.2 Predictability of postoperative pulmonary complications.

Patients undergoing thoracic surgery and more specifically lung resection, have been studied by many authors in attempt to determine which preoperative tests are best predictors of postoperative pulmonary complications. For an overview of the extensive literature on this subject the reader is referred to a recent textbook of Kaplan (1983, part II).

There is general agreement that poor spirometric performance enlarges the risk of pulmonary complications. The pulmonary function tests, however, cannot provide a convenient precise risk factor which can predict whether or not a given patient can tolerate surgery without life-threatening complications. Too many variables exist including the quality of intraoperative and postoperative medical care. Especially in patients undergoing lung surgery, resection of a lung zone with no ventilation but with persistent perfusion would cause the PaO_2 to become better after operation although the spirometric values could be the same as before. To predict more accurately postoperative pulmonary function, radionuclide ventilation-perfusion lung scans can give additional information.

In our clinic the pulmonary criteria for admitting average adult patients to undergo thoracotomy are:

1. The postoperative vital capacity (VC) of the patient can be expected to be at least 2 liters.

2. The postoperative forced expiratory volume in 1 second (FEV_1) can be expected to be 1 liter or more.

3. The preoperative FEV_1 must be at least 30% of the actual VC.

4. The preoperative maximum breathing capacity should be at least 3 times the minute volume at rest.

6.3 Prevention of postoperative pulmonary complications

In both types of surgery (thoracic and upper abdominal), the primary factor which may cause postoperative pulmonary complications is pain. Of course other factors may play a role, but effective pain relief without respiratory depression is essential. Many articles about the effects of epidural analgesia by local anaesthetics on postoperative respiratory function and pain have been published and often a comparison with systemic opiates was made (Simpson, 1961; Muneyuki, 1968; Spence, 1971; Miller, 1976; Bromage, 1978 and 1980). From these studies about the effects of systemic administered opiates, respectively epidural analgesia by local anaesthetics one can conclude:

1. For sufficient analgesia of the thorax, the epidural catheter must be inserted at the high-thoracic level.

2. Pulmonary function parameters are restored better in patients with epidural local anaesthetics than in those receiving systemic opiates. Restoration of pulmonary function is most marked during the early postoperative period.

3. Hypotension, often observed with epidural local anaesthetics is a most troublesome effect, especially in the elderly patient.

4. Analgesia by epidural local anaesthetics is more effective than by systemic opiates.

5. Thoracic epidural analgesia by local anaesthetics is not a safe method for routine use in hospital wards.

More recently opiates have been epidurally applied to relieve pain. From the studies of Bromage (1980), Magora (1980), El-Baz (1984) and Nordberg (1984) the following conclusions can be drawn:

1. For effective analgesia in the thoracic region, the epidural catheter can be inserted in the lumbar region provided hydrophilic opiates are used.

2. Pulmonary function parameters are restored better in patients with epidural opiates than in those receiving systemic opiates.

3. Analgesia by epidural opiates is free of side effects due to sympathetic blockade.

4. Epidural analgesia by opiates gives effective and sometimes rapid analgesia of a long duration in comparison to systemic opiates and local anaesthetics.

5. Depending on the opiate used, epidural analgesia with opiates may be safe for control of pain in hospital wards.

Of course there are other therapeutic interventions and measures possible in preventing postoperative pulmonary complications. With respect to these interventions and measurements (the surgical approach, hyperinflation manoeuvres, postural drainage, transcutaneous electrical nerve stimulation and pharmacological treatment) can be referred to Kaplan (1983, part V).

6.4 Methods of pain relief after thoracic surgery

Finally, the most commonly used methods of pain relief after thoracic surgery will be shortly reviewed.

6.4.1 Systemic opiates

Opiates act on different organ systems in the human body. Most effects of opiates are dose dependent. From the effects on the various organ systems, only the influence on the respiratory system will be discussed (Miller, 1981, chapter 15), because especially these effects are disadvantageous in the postoperative course of

thoracic surgery That opiates decrease the responsiveness to carbon dioxide of the respiratory centers in the central nervous system by decreasing respiratory rate without significantly changing the tidal volume, is generally known. Moreover, opiates alter rhythmicity, impair ciliary motion and may cause bronchoconstriction (morphine) or cause chest wall rigidity (fentanyl) The change in rhythmicity may result in ventilation at constant tidal volume without deep sighs, necessary to prevent atelectasis Impaired ciliary motion can lead to retained secretion and atelectasis It is obvious that opiates are disadvantageous, especially in COPD patients, and that therefore minimal doses supplying adequate pain relief should be administered

6.4.2 Intercostal nerve block

For the relieve of post-thoracotomy pain only unilateral intercostal nerve blocks are required. The most frequently occurring complication of the procedure is pneumothorax Intercostal nerve block influences pulmonary function to a lesser extent than systemic opiates (Cousins, 1980, chapter 25) The main disadvantage is that intercostal nerve blocks give only pain relief for a period of 5-10 hours, and the search for drugs or combinations of drugs to prolong the duration has not yet been very successful

The complexity and poor results of new techniques for intercostal block hindered wide acceptance Some of these techniques are mentioned·

a The technique in which the surgeon leaves a catheter in the intercostal space (Restelli, 1984).

b. Intercostal block by freezing the intercostal nerve (Katz, 1980). With this technique there still is additional need for systemic opiates, but the main disadvantage is a very painful neuritis.

c. A method of pain relief recently described is the continuous interpleural administration of bupivacaine (Reiestad, 1985) From the 56 patients treated with this technique, only 2 patients asked for additional opiates. However, the technique

was not used in patients undergoing thoracic surgery and only 56 patients were involved. Further studies of this technique are needed to evaluate this method.

6.4.3 Analgesia by local anaesthetics

If the epidural catheter is placed at lumbar level to achieve analgesia in the thoracic area, it results in excessive blockade in the pelvic and lower extremity regions. This gives rise to a significant drop of blood pressure and analgesia at thoracic level is often partial. Because of the high incidence of adverse effects associated with thoracic block by local anaesthetics postoperatively, this technique will not have a widespread use in thoracic surgery. In this type of surgery the development of the most troublesome complication (hypotension) is more pronounced, especially in the upright position. Age and fitness of patients certainly may play a role. Also it must be emphasized that after thoracotomies additional opiates are frequently needed to achieve effective analgesia (Conacher, 1983).

6.4.4 Analgesia by epidural opiates

The major advantage of selective blockade by opiates is the absence of sympathetic blockade and consequently absence of postural hypotension. This allows patients to mobilize while avoiding cardiovascular collapse. Also convulsions, the major complication of local anaesthetic blockade, when an i.v. injection or an overdose is accidentally given, do not occur with opiates. Pain relief is adequate compared to other methods used for pain relief (see Chapter 7). The side effects of epidural opiates reflect widespread dispersion of opiates throughout the subarachnoid and ventricular cerebrospinal fluid (respiratory depression, nausea, vomiting, urinary retention, pruritis and sedation). Early and late respiratory depression are major concerns with the use of epidural opiates in spite of their low incidence.

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CHAPTER 7

POSTOPERATIVE ANALGESIA BY EPIDURAL VERSUS INTRAMUSCULAR NICOMORPHINE AFTER THORACOTOMY (I).

7.1 Introduction

Thoracotomy is an operation of considirable risk and causing severe postoperative pain and therefore creates a high need for postoperative analgesia (Parkhouse, 1961; Katz, 1980). Anaesthetic techniques for pulmonary resections and chest wall corrections which improve the safety of surgery and decrease postoperative morbidity will increase the number of patients who can be considered candidates for such surgical therapy. Patients with chronic obstructive pulmonary disease (COPD) have functional disorders (high lung compliance, high airway resistance and also significant ventilation/perfusion ratio inequality). For these patients in particular a technique is required which keeps them away from the ventilator postoperatively. Ventilating the patient postoperatively, introduces the risk of infections, the risk of barotrauma and the deconditioning of the respiratory muscles which might result in difficult weaning of the patient from the ventilator.

The aim of the study is:

1. to describe the safety of the high-thoracic epidural anaesthesia technique with local anaesthetics followed by postoperative analgesia with epidural opiates (epidural or EPID group), and compare this thechnique to the balanced intravenous anaesthesia and postoperative analgesia by means of

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intramuscular injection of the same opiates (IM group)

2 to compare the postoperative analgesia and complications in the IM group and the EPID group

The results of this study are described in two parts

I. The first part concerns the general parameters of various surgical groups and evaluates the high-thoracic epidural approach and its sequelae It also compares the postoperative analgesia in the IM group versus the EPID group

II. The second part investigates the differences in postoperative opiate consumption and its consequences in the IM versus the EPID group It compares the postoperative $PaCO_2$ in the two groups as being the most important parameter for adequate ventilation
Finally the postoperative complications are compared between the two groups:
a. the complications specific for the lungs,
b. the complications due to the general effects of opiates

7.2 Patients and methods

The patients were informed by the investigator and gave their consent for the study For postoperative analgesia by i.m. or epidural route nicomorphine (Vilan®, Nourypharma, Oss, The Netherlands, preservative free) was used The investigation comprised 163 patients 80 patients got postoperative analgesia by i.m injections of nicomorphine, 83 patients through the high epidural catheter The patients were randomly allocated either to the IM group or the EPID group.
Three groups (I, II and III) are distinguished according to the types of surgery

I. Patients undergoing a lobectomy, segmental resection of the lung or a pneumonectomy (n=78),

II. Patients scheduled for chest correction: pectus excavatum (funnel chest), pectus carinatum (chicken breast) or pectus arcuatum (pouter pigeon) (n=67),
III. Patients selected for a pleurectomy, bullectomy or thoracotomy for diagnostic reasons (n=18).
All 163 patients were operated by the same two surgeons.

The ASA class varied from class I (mainly surgery group II) to class IV. The diagnosis COPD was defined to exist in patients being under control of a pulmonologist, having obstructive lung disease confirmed by lung function tests and receiving chronic drug therapy for their disease.

Anaesthesia

The IM group was premedicated with nicomorphine 0.1 mg/kg i.m. and droperidol 5 mg i.m. one hour before the operation. Anaesthesia was induced by a sleeping dose (5 mg/kg) of pentothal i.v. followed by succinylcholine (1 mg/kg) to facilitate intubation. Anaesthesia was maintained with N_2O/O_2 in the ratio 1/1, pancuronium 4-6 mg, and droperidol 5-10 mg i.v.. Halothane not more than 0.5 % was added if necessary. Analgesia during the operation was controlled by giving nicomorphine 0.1 mg/kg i.v. (never exceeded 10 mg).

The EPID group was premedicated with diazepam 5-10 mg orally and 0.5 mg atropine i.m. one hour before the operation. Anaesthesia was induced and maintained in the same way as the IM group. Analgesia during the operation was provided with epidural bupivacaine (Marcaine®) 0.5 % or 0.25 % with adrenaline 1:200,000 in doses of 6-12 ml (depending on age, length and weight). The epidural was inserted in the awake, sitting, at the T3-T4 level. The paramedian approach was performed in 75 cases; only in 8 cases the median approach was applied. The hanging drop technique was used to identify the epidural space. The catheter was directed cephalad and advanced 3-4 cm. The patient was then placed supine and a initial test dose of 3 ml lidocaine 2 % was injected through the catheter. The block was tested 15 minutes later. Usually the segments T3-T6 were blocked by this test dose. The block was also tested after the

final dose At the conclusion of surgery none of the patients of either group were antagonized, neither for the neuromuscular block nor for a ventilatory depression by nicomorphine

Postoperative management

To obtain satisfactory pain relief nicomorphine was given, on patients request only, 0.1 mg/kg i m (in the IM group) or 4-6 mg nicomorphine diluted in 8-12 ml of dextrose 5% in the epidural catheter (EPID group). A postoperative pain assessment was obtained from 56 patients (23 in the IM group and 33 in the EPID group) four days after the operation The pain assessment was introduced into the protocol at a later stage The patients scored their pain as pain free, slight, moderate or severe.

The pain relief was also assessed by the medical team, consisting of medical and nursing staff attendants as well as physio-therapists Their score was graded as excellent, sufficient, or unsatisfactory pain relief

Statistical analysis

The statistical calculations were carried out using the SPSS routine package (SPSS Inc., Chicago, Illinois). In the complete data set two factors are distinguished in the analysis of variance (ANOVA)·

1 anaesthesia (IM/EPI),

2. surgery type (I/II/III)

If a comparison is made between two group means Student's t-test (T-test) is applied Finally, comparison of frequencies is performed with a χ^2-test, with the exception of a 2 x 2 table, where a Fisher's exact test (FET) is used

Assessment of data

The following items were studied:

Treated in part I:

1. Demographic data: length, weight, sex, age, various drugs used by the patient and the type of operation,
2. The thoracic epidural catheter technique and its sequelae,
3. postoperative pain as assessed by the patient as well as by the medical team,

Treated in part II:

4. nicomorphine requirements,
5. pre- and postoperative $PaCO_2$,
6. postoperative complications of surgery,
7. complications due to the general effects of opiates,
8. cardiac arrythmias.

7.3 Results

1. Demographic data.

Age. The characteristics of the two analgesia groups of patients sub-divided in three surgery groups are listed in table 1. There is a significant difference in age for group II as compared with groups I and III (ANOVA $p<0.001$).

Also within these groups there is a significant difference between those who received their postoperative analgesia i.m. or by epidural catheter (ANOVA $p=0.002$). The patients in the EPID group are older.

Sex. From table 2 it follows that there are more men than women. Since most of the patients in surgery group I came for treatment of carcinoma of the lung this is not surprising. There is no significant difference in sex distributions between the various groups.

Weight. In table 3 the mean weights of patients in the six sub-groups are listed. Clearly there is a correlation between age (table 1) and weight (table 3).

Table 1: Age.

Ages (years) in the various operation groups, average values with standard deviations in parentheses.

	IM	EPID
I	54 (17)	61 (11)
II	14 (6)	21 (11)
III	41 (10)	44 (18)

ANOVA Main effect of IM/EPID groups p=0.002
Main effect of I/II/III groups p<0.001

IM = intramuscular; EPID = epidural.

Table 2: Sex.

Group size and distribution of sexes over the various groups.

	IM			EPID			
group	total	female	male	total	female	male	FE-test(*)
I	38	8	30	40	9	31	ns
II	34	11	23	33	6	27	ns
III	8	1	7	10	3	7	ns
Total	80	20	60	83	18	65	

*) Fisher's exact test for significant difference of sex-distribution between IM/EPID groups.
IM = intramuscular; EPID = epidural.
ns = not siginificant.

The presence of obesity was expressed in a weight/length ratio, defined as:

(weight in kg)/(length in cm - 100).

If there is any overweight this ratio will be greater than 1.1 (Bromage, 1978, chapter 11). Obesity implies a higher risk to develop postoperative pulmonary complications (Harman, 1979).
There is a significant difference in the weight/length ratio between

Table 3: Weight.

Average values and standard deviations (within parentheses) of weights (kg) in the various groups.

	IM	EPID
I	70 (14)	72 (10)
II	45 (15)	62 (10)
III	70 (12)	69 (15)

IM = intramuscular; EPID = epidural.

Table 4: Weight/length ratio.

Average values of the weight/length ratio (kg/cm), as defined in the text, and their standard deviations in the various groups.

	IM	EPID
I	1.01 (0.16)	0.99 (0.13)
II	0.73 (0.09)	0.77 (0.08)
III	0.97 (0.17)	0.91 (0.16)

ANOVA Main effect I/II/II groups	$p < 0.001$
T-test difference of integral IM/EPID groups	$p = 0.83$
T-test difference of integral COPD/non-COPD	$p = 0.044$

IM = intramuscular; EPID = epidural.
COPD = chronic obstructive pulmonary disease.

the various surgical groups. The weight/length ratio in group II is less than in the others (ANOVA $p<0.001$, table 4). However, between the IM and the EPID group there is no significant difference ($p=0.83$). But, if we look at this ratio in COPD patients there is a significant overweight in comparison to non-COPD patients (T-test $p=0.04$).

2. The thoracic epidural catheter technique and its sequelae.

Ninety-seven patients received an epidural catheter (table 2). In 14 patients the catheter was either plugged or accidentally pulled out, or patients got nicomorphine intramuscularly by mistake. These patients were removed from this study, leaving 83 patients in the EPID group.

The hanging drop test was positive in 97% of the cases. Only one spinal tap occurred, although most of the catheters were inserted by supervised residents.

Vasopressors were given if there was a decrease of systolic arterial blood pressure of more than 25%. In 5 cases (6%) a vasopressor (ephedrine sulfas) was needed after giving the bupivacaine 0.5 % with adrenaline 1:200,000.

Neither a continuous infusion of dopamine nor of dobutamine was necessary. After the application of epidural nicomorphine no significant drop of arterial blood pressure was observed.

No inadvertent intravascular injection of the local anaesthetic occurred.

3. Postoperative pain.

Table 5 shows the results of the pain assessment by the patient on the fourth day after the operation.

Table 5: Pain assessment by patients.

Postoperative pain assessment four days after surgery by the patient. Frequencies of scores in the 23 intramuscular (IM) and 33 epidural (EPID) patients.

score\group	IM	EPID
pain free	11	20
slight pain	10	9
moderate pain	2	4
severe pain	0	0

More than 55% assessed the first three postoperative days as pain

free, 33% graded their pain as slight and 10% as moderate. No patients in either analgesia group indicated severe pain. It should be realized, that one is dealing with a judgement about the integral postoperative three day period. A score of "mild" or "pain free" does not imply, that the patient never experienced severe pain (see below). Although (with these low numbers) these scores are not significantly different between the analgesia groups, the number of patients scoring "pain free" is greater in the EPID group (60%) than it is in the IM group (47%).

In table 6 the pain relief assessment by the medical team is listed.

Table 6: Pain relief assessment by the medical team.

Postoperative pain assessment four days after surgery by the team. Frequencies of scores in 23 intramuscular (IM) and 33 epidural (EPID) patients.

score\group	IM	EPID
excellent	13	23
sufficient	8	9
unsatisfactory	2	1

In the EPID group 70% of the patients were judged to have had excellent pain relief, compared to 56% in the IM group.

The onset of pain relief by nicomorphine was also studied in the two analgesia groups. All patients evaluating the postoperative pain (table 5) on the fourth day were also involved in the study of onset of pain relief. At times 0, 5, 15 and 30 minutes after the administration of nicomorphine along either route patients evaluated their discomfort as mild, moderate or severe. The development of pain relief obtained in this way is depicted in figure 7.1

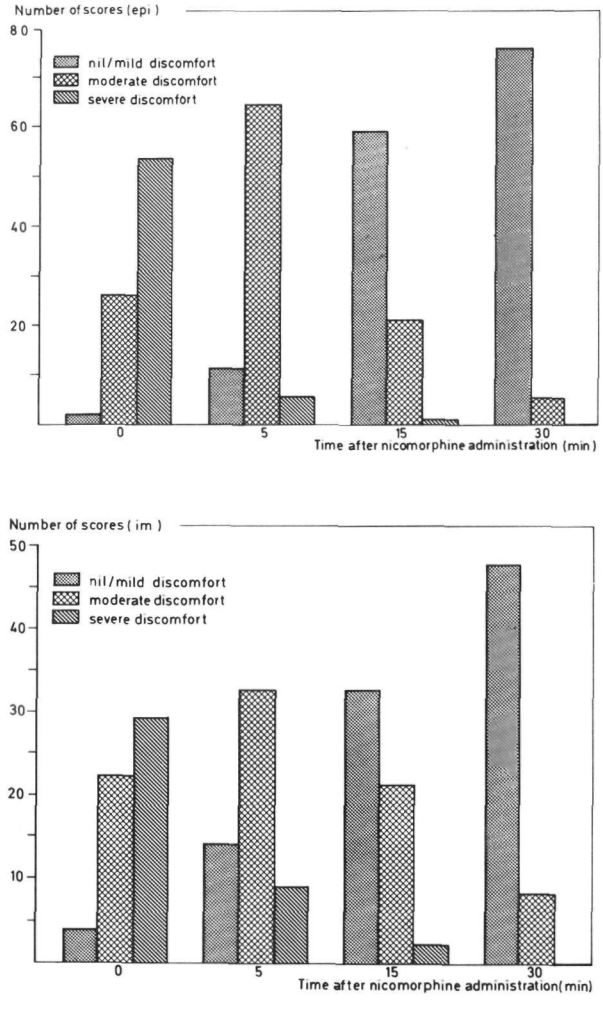

FIG. (7.1) *The onset of the analgesic effect of nicomorphine. Histograms of pain scores at 0, 5, 15 and 30 minutes after the administration of nicomorphine in the EPID group (top, total of 85 scores in 33 patients) as well as the IM group (bottom, total of 55 scores in 23 patients).*
Note that a single patient possibly supplies more than one evaluation data point, because pain assessment was acquired several times.

Epidural catheter technique and its sequelae.

If an epidural catheter, meant for postoperative pain relief, is already inserted before the induction of anaesthesia it is logical to use it also for application of a local anaesthetic peroperatively. It has the disadvantage of introducing a dissimilarity between the IM and EPID groups beforehand. On the other hand administration of i.v. nicomorphine during the operation might also obscure the advantages of epidural application postoperatively.

Epidural local anaesthesia prevents afferent impulses from reaching the central nervous system during the operation and prevents transmission of inappropriate efferent signals to target organs such as the bronchial smooth muscle in the case of thoracic surgery.

The only contra-indication of a high-thoracic epidural catheter technique by local anaesthetics (next to the normal contra indications for epidural analgesia in general) is the use of β-blocking agents. This combination showed in another study of ours severe bradycardias depending on the local anaesthetic used (to be published).

Postoperative epidural application of opiates limits the presence of the drug to its site of greatest effectiveness. For this reason we compared this technique with the general anaesthesia technique. The catheters used were from Arrow/Racz, they are of a flexible guide wire type and cannot kink. The catheter is also clearly visible on X-ray, so we knew exactly at which thoracic level the catheter was placed. If one inserts the catheter in the awake patient, the advantage is that the patient can indicate whether he/she feels pain or other sensations on insertion.

The sitting position is preferable for several reasons:

1. The thoracic epidural pressure is more negative in this position (Bromage, 1978, chapter 5).

2. The spinous processes are more clearly visible and better palpable because the soft surface of the bed does not affect the spinal curvature.

3. For COPD patients, especially it is more comfortable to sit upright.

4. Particularly in obese patients the midline is more easily identified.

The high-thoracic epidural approach has several advantages.
Part of the afferent nervous input from lungs and airways enter the central nervous system along the sympathetic nerves to the upper four thoracic segments (Widdicombe, 1963; Harman, 1979). The afferent input blockade can prevent and even cure bronchospasm per- as well as postoperatively (Bromage, 1978, chapter 10). Endobronchial toilet can be accomplished without severe circulatory reactions (Shuji, 1982).

Otton (1966) describes the potential hazards of high epidural blockade of the cardiac sympathetic nerves most precisely. Their blocking causes an indirect cardiac depression, reflected by a fall of cardiac index and heart rate and a rise of central venous pressure. Otton (1966) in his experiments placed the catheter at C7-T1 level and injected mepivacaine 1 % plain 60-80 mg. Especially with mepivacaine 2% with adrenaline 1:200,000 severe bradycardia's can be expected, which will only react on isoprenaline. In our study with the catheter at level T3-T4 and using bupivacaine 0.5 % with adrenaline 1:200,000, very few cardiovascular changes were seen. A possible explanation for this may be the addition of adrenaline with its β-stimulating effects (Bonica, 1971), or the specific autonomic system saving effect of bupivacaine in comparison to other local anaesthetics. This sparing effect of bupivacaine is also seen when it is used in spinal anaesthesia (Sheskey, 1982).
With a sensory block from T1-T10, as performed in this study, the resistance and capacitance vessels of the splanchnic and leg vascular beds are not blocked, and this makes the drop of arterial

pressure not as pronounced as when the lumbar and sacral nerves are also involved. It is striking that in only 3 of the 83 patients were the cervical root segments involved after the epidural injection of bupivacaine. Therefore we suspect even in the supine position a preferential downward spread of the solution with the catheter at the T3-T4 level. This also supports the insertion of the catheter at this and not at a lower level.
Advancing the catheter more than 4 cm is not recommended. The catheter can curl up or even pass outward through an intervertebral foramen into the paravertebral space (Bromage, 1978, chapter 7). This happened once in our study.

Postoperative pain. The scores by the medical team (table 6) are negatively influenced by surgical group II consisting of young healthy patients. For surgical reasons they had to stay in a supine position during the first five days after surgery. The fact that they were less sedated by the epidural nicomorphine than with the i.m. nicomorphine made them complain about pain and feel uncomfortable. If the scores of surgical group I are taken into account only, the outcome is significantly more in favour of the EPID group.
Nicomorphine provides effective analgesia of a rapid onset when given either intramuscularly or by the epidural route (fig. 7.1). Already within 5 minutes after injection the number of patients with severe pain dropped significantly. The decrease is even more pronounced in the EPID group than it is in the IM group. The immediate onset of pain relief in the EPID group is probably caused by a universal effect of nicomorphine absorbed in the venous plexus (Chauvin, 1981).
In conclusion: the anaesthesia technique as used in the EPID group, provides a safe and circulatory stable procedure. Assessments of pain relief, by the patients as well as by the medical medical team, are not significantly different for the two analgesia groups.

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CHAPTER 8

POSTOPERATIVE ANALGESIA BY EPIDURAL VERSUS INTRAMUSCULAR NICOMORPHINE AFTER THORACOTOMY (II).

8.1 Introduction

Pain relief after thoracotomy is difficult to accomplish. Four main techniques have been described:
Firstly, postoperative epidural analgesia with local anaesthetics. This technique has many adverse effects of which hypotension is most troublesome (Griffiths, 1975; James, 1981; Conacher, 1983).
Secondly, the use of parenterally administered opiates. This administration has known disadvantages of which ventilatory depression, nausea, vomiting and inadequate pain relief are well recognised (Conacher, 1983).
Thirdly, intercostal nerve block by local anaesthesia (Delikan, 1973; Galway, 1975) or by cryoanalgesia (Katz, 1980). With these techniques there still may be an additional need for opiates.
Fourthly, epidural opiates can be given.
The aim of this study is to evaluate possible clinical advantages or disadvantages of two techniques described in part I; the epidural analgesia technique (EPID) in comparison to the intramuscular technique (IM).

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Published in Acta Anaesth. Scand. 29: 577-582, 1985.

8.2 Patients and methods

The patient population (n=163) and the preoperative, peroperative and postoperative anaesthetic management were described in part I.

Arterial blood samples for analysis of $PaCO_2$ were taken:

- the day before operation,
- the day of operation (defined as day 1) 30 minutes after the operation, 14.00, 18.00, 20.00 and 24.00 h.
- the first and second days after operation (defined as days 2 and 3) at 9.30, 14.00, 18.00, 20.00 and 24.00 h.

If the respiratory rate fell below 14/minute or the previous arterial bloodgas analysis showed substantial (>10 %) increase in $PaCO_2$, additional blood samples were taken.

X-rays of the thorax were taken preoperatively, immediately postoperative and once every day. Thereafter the X-rays were specifically screened for atelectases. The reporting pulmonologist did not know which treatment for pain relief was given to the patients.

Bronchoscopic tracheo-bronchial toilet (BTT) was performed if there was a combination of massive radiologically verified atelectasis and a deteriorating bloodgas analysis.

The occurrence of any cardiac arrythmias after surgery (different from those arrythmias observed before the operation) was specifically investigated.

The item "complications due to general effects of opiates" was introduced in the protocol at a later stage. The assessment of drowsiness took place on day 2 to avoid the influence of drugs given for premedication and anaesthesia. Other "complications due to the general effects of opiates" were investigated on days 1, 2 and 3.

Assessment of data

In part I demographic data, the thoracic epidural technique and its sequelae and the postoperative pain assessment have been discussed (as items 1,2 and 3).

In this part we will focus on:

4. the nicomorphine requirements,
5. pre- and postoperative $PaCO_2$, as well as the difference ($\Delta PaCO_2$),
6. postoperative complications of surgery,
7. complications due to the general effects of opiates (drowsiness and other complications),
8. cardiac arrythmias.

Statistical analysis. Statistical analysis by analysis of variance (ANOVA), Student's t-test (T-test) and Fisher's exact test (FET) has been discussed in part I.

8.3 Results

4. Nicomorphine requirements.

Nicomorphine requirements on day 1, 2 and 3 and the total amount required are shown in figure 8.1.

Significant differences in nicomorphine requirements between the analgesia groups (EPID/IM) on all three days were found. The highest nicomorphine requirement was on day 2, in all surgical groups.

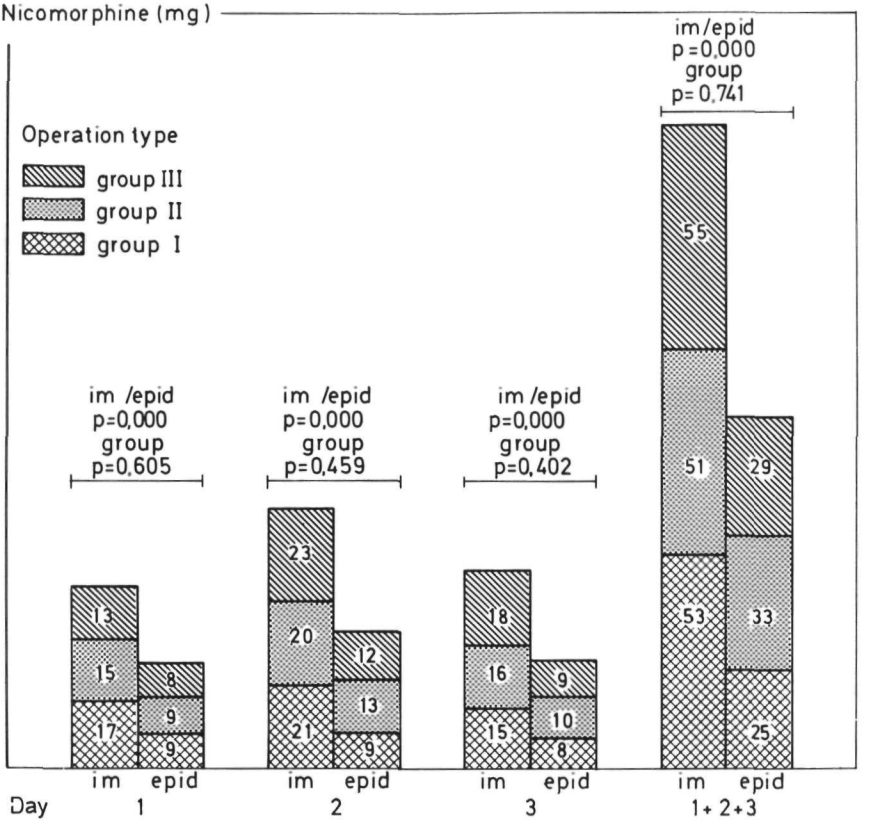

FIG. (8.1) *Nicomorphine dose requirements of the IM and EPID group in the various surgical groups (I, II, III) on day 1, 2 and 3 and the total of nicomorphine required on day 1, 2 and 3. Statistical analysis by ANOVA (n=163). The amount of nicomorphine required of each sub-group is indicated by figures in the squares. The significances (p-values) are indicated at the top of the figure for the comparison between the analgesia groups (im/epid) and for the surgical groups (group I, II and III).*

5. Pre- and postoperative $PaCO_2$.

Average values of $\Delta PaCO_2$, defined as the highest $PaCO_2$ of the patient on day 1, 2 or 3 minus his (her) preoperative value of $PaCO_2$, are shown in figure 8.2

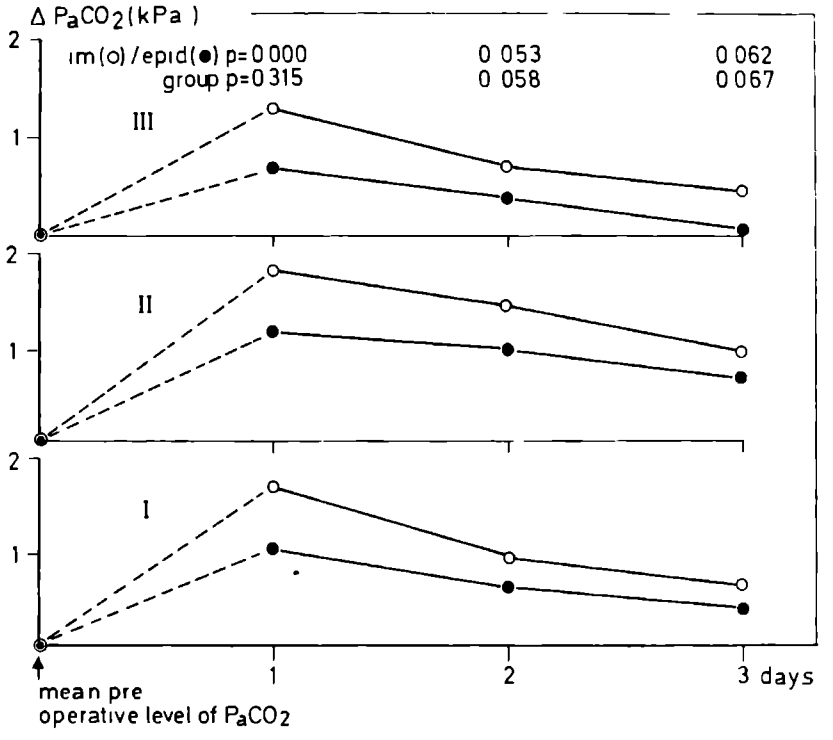

FIG. (8.2) *Average values of $\Delta PaCO_2$ (kPa) in the various surgical groups (I, II, III). $\Delta PaCO_2$ is defined as the highest $PaCO_2$ measured on day 1, 2 or 3 of a patient minus his (her) preoperative value of $PaCO_2$ in kPa. Statistical analysis by ANOVA (n=163). The average standard deviation of the 18 data points in the figure amounted to 0.9 kPa. The significances (p-values) are indicated at the top for comparison of the analgesia groups (im(o)/epid(•)) and of the surgical groups (I, II and III).*

The $\Delta PaCO_2$ in the IM group is higher than the $\Delta PaCO_2$ in the EPID group on all three days. This difference is significant only on days 1 and 2 (ANOVA p=0.062). Between the surgical groups (I,II and III) there is no significant difference in $\Delta PaCO_2$. On day 2 group II's $PaCO_2$ value is returning more slowly to its preoperative level than the other groups. On that day the difference between the surgical groups nearly reaches significancy (p=0.058).

6. The postoperative complications of surgery

Atelectasis. The number of radiologically verified atelectases on the first three days postoperatively in the three surgical groups in total and subdivided in COPD patients and non-COPD patients are depicted in figure 8.3

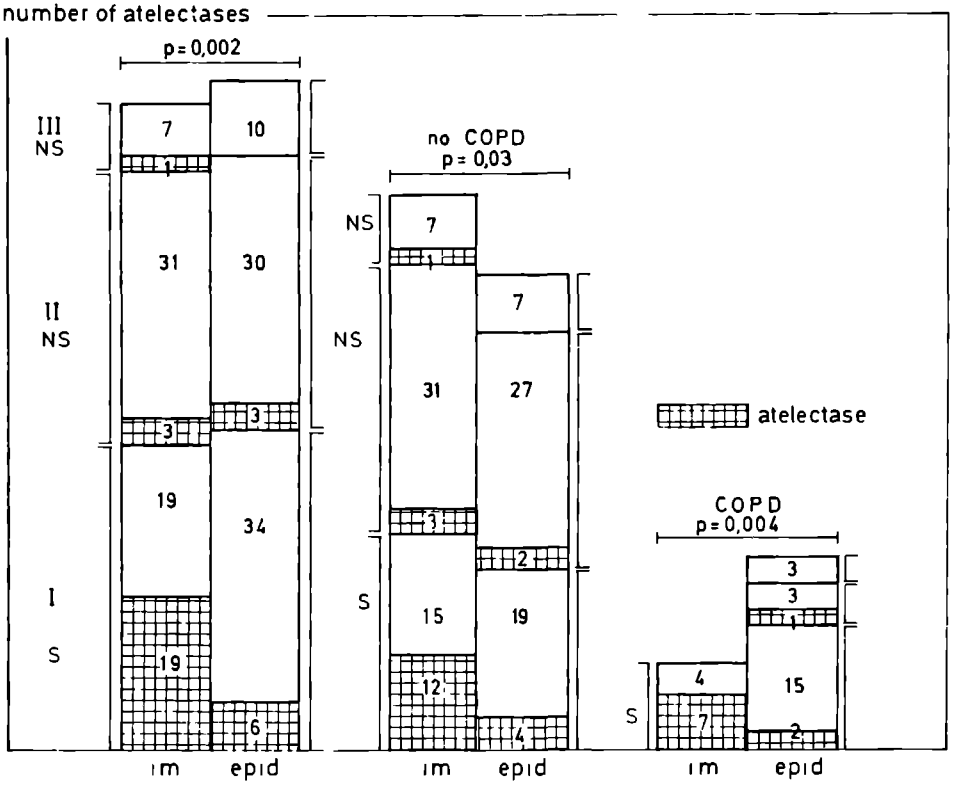

FIG. (8.3) *Histogram of the total number of atelectases on the first three postoperative days in the various surgical groups (I, II, III). The numbers of patients are also indicated by figures in the histogram. The total number of patients is then subdivided in patients with and without COPD (at the right). Statistical analysis (p-values, S: $p < 0.05$, NS: $p > 0.05$) by FET.*

If a patient developed several atelectases at different times this was considered as a single count in the statistical analysis. There are significantly fewer atelectases in the EPID group (FET p=0.002) compared to the IM group. Unintentionally the EPID group contained more patients with COPD than did the IM group (figure 8.4).

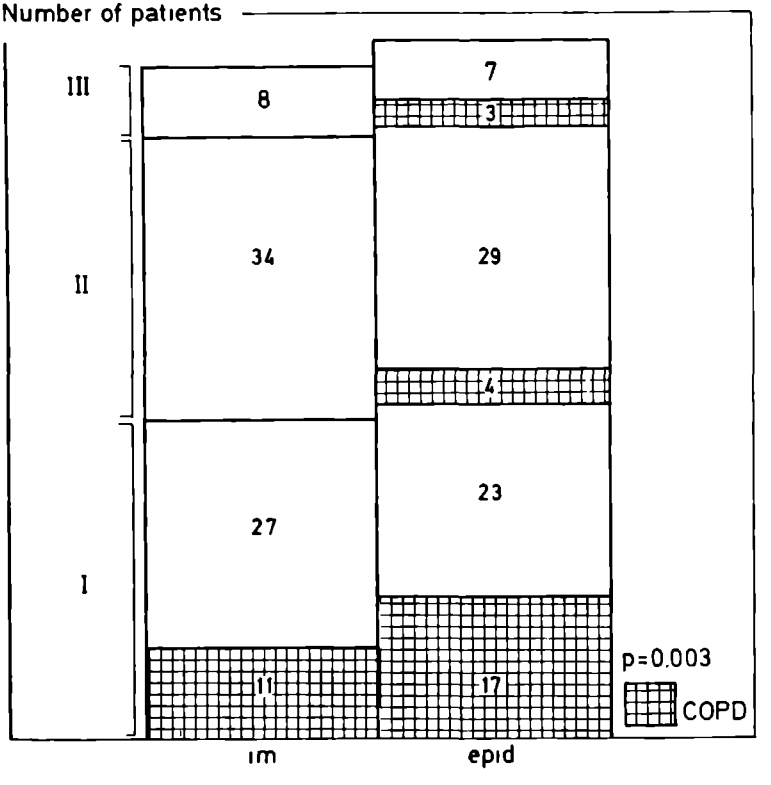

FIG. (8.4) *Distribution of COPD patients over the various groups. The number of patients (COPD and non-COPD) in the various analgesia (IM/EPID) and surgical groups (I, II, III), are indicated by figures in the histogram.*

BTT. The number of BTT's performed by the pulmonologist, again subdivided in patients with and without COPD, are depicted in figure 8.5

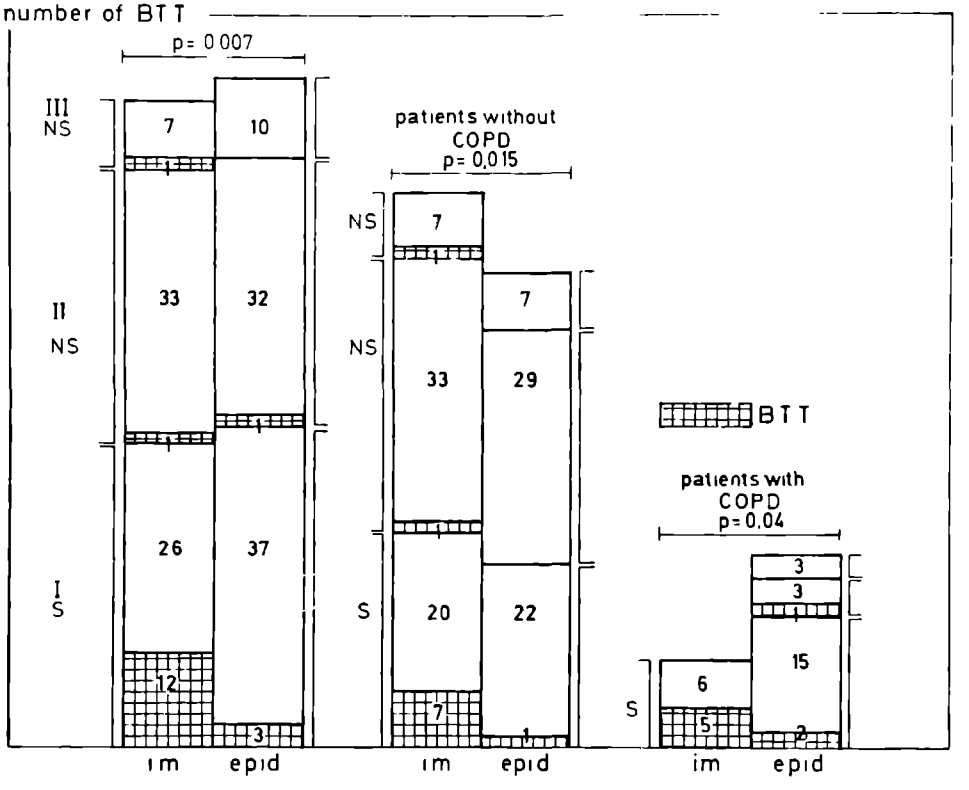

FIG. (8.5) *Histogram of bronchoscopical tracheobronchial toilets (BTT) performed on the first three days in the various surgery groups (I,II and III). The frequencies are also indicated by figures. The total number of patients is then subdivided in patients with and without COPD. Statistical analysis (p-values, S: $p < 0.05$, NS: $p > 0.05$) by FET.*

The statistical difference between the EPID and IM groups in this respect was also highly significant (FET p= 0.007).

For the IM group without COPD most of the atelectases developed on the first day (n=8) and on the third day (n=6). For the IM group with COPD most of the atelectases developed on the second day (n=5). In the epidural group with and without COPD there was an equal distribution in the development of atelectases over the three days.

7. Complications due to the general effects of opiates.

Drowsiness: A number of patients were markedly drowsy after administration of nicomorphine in both anaesthesia groups (table 1).

Table 1: Drowsiness.

General complications of opiates: drowsiness
Number of drowsy patients in the IM and EPID groups.

	IM	EPID
no drowsiness	12	27
markedly drowsy	15	11
FET p = 0.05		

Even from this relative small number of patients one can see that the EPID group was significantly less drowsy.

Other complications: The other complications are listed in table 2. The incidence of urinary retention in the EPID group is significantly higher than in the IM group. Nausea and/or vomiting was not specific for any particular route of administration.

8. Cardiac arrythmias

There were no significant differences in this respect between the patients who got pain relief by i.m. or by epidural nicomorphine. As expected most of the cardiac arrythmias were in group I.
Sixty-eight percent of the patients who were using cardiac drugs

Table 2: Other complications than drowsiness.

Incidence of complications due to general effects of opiates in the IM and EPID anaesthesia groups (n is number of cases studied for each complication).

	IM		EPID		sign
	n	Compl	n	Compl	
Heart rate < 60 beats/min	80	0	83	1	ns
Mean art press drop > 20%	80	0	83	1	ns
Resp rate < 14/min	80	1	83	5	ns
Nausea (*)	67	18	64	13	ns
Vomiting (*)	66	13	64	7	ns
Itching (*)	31	0	40	3	ns
Urinary retention (*)	69	31	70	50	0.027

Statistics by FET.
(*) The evaluations of these items has been introduced into the protocol at later stages in the study.

before the operation got cardiac arrythmias after the operation. From those patients who did not use any drugs before the operation only 38 % got cardiac arrythmias after surgery.

8.4 Discussion

Dose requirements of nicomorphine: Opiates have important side effects regardless their route of administration (Chauvin, 1981). This implies that reduction of opiate dose is advantageous, especially for patients with COPD (Tarhan, 1974). The significantly smaller requirements of nicomorphine in the EPID group has important consequences for the complications due to opiates. Postoperatively, patients tend to have an abnormal ventilatory pattern with diminished or absent sighing (Harman, 1979). This pattern of breathing is potentiated by the administration of opiates. Egbert (1964) found morphine to cause a profound reduction in the incidence of spontaneous deep breaths and suppression of the cough reflex.

Ventilatory depression: The ventilatory depression is a potentially very dangerous side effect of opiates. In studies investigating the ventilatory depression after application of epidural opiates, the epidural catheter was inserted at lumbar or low thoracic level and the drugs used were morphine or diamorphine (McCaughey, 1982; Möller, 1982; Rybro, 1982; Jacobson, 1983; Kafer, 1983).
However, in this study the catheter was inserted at T3-T4 level (in one patient it was even inserted at T1-T2) and there were no signs of ventilatory depression (fig 8.2).
Delayed ventilatory depression was reported following intra-thecal injection of morphine (Glynn, 1979; Liolos, 1979; Davies, 1980a; Davies, 1980b; Gebert, 1980; Mok, 1981) and possibly after diamorphine intrathecally (Barron, 1981) but also after epidural pethidine (Scott, 1979). Combined administration of systemic opiates with local anaesthetics may add to the risk of ventilatory depression (Boas, 1980; Barron, 1981; Holmboe, 1982). This danger therefore is not exclusively related to epidural opiate administration. Ventilatory depression was not found to be a predominant aspect in epidural injection of nicomorphine (Pinckaers, 1982). Whether this is due to nicomorphine or to the use of hyperbaric dextrose 5 % as the diluent needs further study.

We intentionally did not fix the time of taking blood samples for gas analysis after epidural injection of nicomorphine, because with the tip of the catheter at T2-T3 level, we did not know at what time the ventilatory depression would be most prominent. By taking fixed times we avoided a systematic error in determination of bloodgases due to a possible ventilatory depression.

In six patients the respiratory rate dropped below 14/min, five of them were in the EPID group (3 in group I, 2 in group II), one was in the IM group. None of the EPID patients had a $PaCO_2$ of more than 6.8 kPa at any time, while the IM patient had the second day a $PaCO_2$ of 8.0 kPa. Interestingly the low breathing frequency seen sometimes with the epidural nicomorphine did not lead to an elevated $PaCO_2$. This low breathing frequency rather indicates the painless and deep breathing of these patients.

The patient with the catheter tip at the T1 level had a preoperative $PaCO_2$ of 5.9 kPa. His highest $PaCO_2$ levels were 7.3 kPa on the day of operation, on the second day 6.1 kPa and on the third day 5.9 kPa.

Pulmonary complications: The number of postoperative complications of surgery is significantly lower in the EPID group, especially in COPD patients. Similar results were found by Rybro (1982) in a much smaller study in healthy non-COPD patients for upper abdominal operations.
The fact that, in the present study fewer complications in the EPID group are seen is even more striking if we account for the facts that:

1. There were more epidural patients in the high risk COPD group (part I).

2. There was a significant overweight in the COPD group (part I).

3. The patients in the epidural group were significantly older (part I).

Each of these factors makes the risk of pulmonary complications greater (Harman, 1979). A recent prospective study of Garibaldi (1981) shows a 17.5% over-all incidence of post operative pneumonia in patients undergoing elective thoracic, upper abdominal and lower abdominal surgeries. In our study only one seven year old girl of group II developed a pneumonia on the third postoperative day. Even in upper abdominal surgery an incidence of more than 25% for postoperative atelectases is seen (Harman, 1979). We found the same incidence in the IM group, but in our EPID group the percentage is 11%.
The mortality from respiratory failure alone in COPD patients has been reported to be four times higher than death due to all causes in non-COPD patients in a general surgical population (Tarhan, 1974). One death from respiratory failure occurred directly after surgery in our study. This patient suffered from lung fibrosis and

came for an open lung biopsy. By lack of data this patient was not included in the analysis. None of the patients in either analgesia group needed to be ventilated postoperatively.

Complications due to the general effects of opiates: Less drowsiness in the EPID group is a disadvantage for the patients in group II. It was requested by the surgeon that patients with this kind of bony deformities, remain supine for five days postoperatively. This sometimes was not acceptable for patients in group II, and they had to be sedated for this purpose. Normally, however, being less drowsy is an advantage, especially in thoracic operations because of better cough reflex and better cooperation with physiotherapy.
The single patient in table 2 with a heart rate below 60 beats/minute and a mean arterial pressure decrease of more than 20% after injection of the nicomorphine epidurally was a patient who developed a sick sinus syndrome postoperatively, and received a pacemaker for that reason.

Incidence of urinary retention was significantly higher in the EPID group. The occurrence of urinary retention is thought to be the result of binding of nicomorphine to opiate receptors localized in the sacral segments. This might depress the parasympathetic preganglionic nerves, thus effecting para sympathetic inhibition (Torda, 1980). One should expect thoracic epidural anaesthesia and analgesia by nicomorphine to produce very little disturbance of the bladder function. The incidence of urinary retention in our study is high (71 %) compared to the 21 % reported by Dirksen (1983) after epidural administration of the same drug 10 mg. An explanation may be the very high percentage of urinary retention in the group II patients, who had to stay in the supine position for 5 days for surgical reasons.

In conclusion: it appears that, in spite of the high position of the epidural catheter, ventilatory depression does not occur in the EPID group with this particular drug. For the complications due to general effects of opiates it is striking, that the EPID group shows significantly less drowsiness, but also significantly more urinary

retention than the IM group. With the anaesthesia and analgesia technique used in the EPID group, the most hazardous and frequent complication of surgery (atelectasis) occurs significantly less than in the IM group.

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CHAPTER 9

POSTOPERATIVE ANALGESIA BY EPIDURAL VERSUS INTRAMUSCULAR NICOMORPHINE AFTER THORACOTOMY (III).

9.1 Introduction

In the previous studies (Chapters 7 and 8) one hundred and sixty-three patients subjected to three different types of thoracic operations were allocated randomly either for balanced intravenous anaesthesia including i.v. opiates with postoperative intramuscular opiates (intramuscular group) or for balanced intravenous anaesthesia without i.v. opiates but with high-thoracic epidural regional block during the operation followed by epidural nicomorphine postoperatively (epidural group). Since both the intramuscular and epidural group received different analgesics during and after operation, it is impossible to conclude that the better results in the epidural group (Chapter 8) were due to either the bupivacaine administered during the operation epidurally or the nicomorphine administered epidurally postoperative.
To investigate this we studied two complementary analgesic groups, and tried to find the best combinations of analgesia during and after operations with respect to postoperative morbidity (Table 1). The aim of the study was to reduce the number of postoperative pulmonary complications by changing the type of analgesia during and after the operation.
The groups in table 1 numbered 1 and 2 have been discussed in the parts I and II (Chapters 7 and 8), from here on called *first study*. The numbers 3 and 4 are discussed in this part III, from here called *second study*, and are again named intramuscular and epidural group. In both studies the attention is focussed on the postoperative

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Table 1: Analgesia groups.

Type of analgesia used during and after the operations. The numbers 1 and 2 have been discussed in the parts I and II (1,2), the numbers 3 (EPID group) and 4 (IM group) are discussed in this part III. Drugs for analgesia used are nicomorphine (N.M.) and bupivacaine (Bu).

	During operation	
	i.v. N.M.	epid. Bu
Postoper. i.m. N.M.	1	4
Postoper. epid. N.M.	3	2

analgesic regime; in the discussion of this study, however, the peroperative analgesic regime will be included and the integral data of both studies analysed. Eleven patients from the *first study* intramuscular group (group 1 in table 1) belong in fact in the intramuscular group of the present study (group 4 in table 1). These patients received bupivacaine during surgery by epidural catheter, but, due to loss of the catheter, they had to be administered nicomorphine i.m. postoperatively. It has been checked and confirmed that this transfer did not affect any of the conclusions drawn in part I and II.

9.2 Patients and methods.

The patients were informed by the investigator and gave their consent for the study. For postoperative analgesia by the i.m. or epidural route, nicomorphine (Vilan®, Nourypharma, Oss, the Netherlands, preservative free) was used. This investigation comprised 129 patients: 71 patients received postoperative analgesia by i.m. injections of nicomorphine (IM-group), and 58 patients through the high epidural catheter (EPID-group). The patients were randomly allocated to either the IM group or the EPID group.
Three groups (I, II and III) are distinguished according to their types of surgery:

I. Patients undergoing a lobectomy, segmental resection of the lung or a pneumonectomy (n = 68).

II. Patients scheduled for chest corrections: pectus excavatum (funnel chest), pectus carinatum (chicken breast) or pectus arcuratum (pouter pigeon) (n = 43).

III. Patients selected for a pleurectomy, bullectomy or thoracotomy for diagnostic reasons (n = 8).

The ASA class varied from class I (mainly surgery group II) to class IV. In all patients, both from *first* and *second* study, pulmonary function tests have been performed before surgery. Mean values of these tests are listed in table 10.
The COPD (Chronic Obstructive Pulmonary Disease) patients, in both studies, consist of a heterogenous population (chronic obstructive bronchitis, asthmatic bronchitis and emphysema) having two phenomena in common: their pulmonary function tests show an expiratory obstruction, and they have a percentual enlargement of the functional residual capacity in relation to the total lung capacity.
All 129 patients were operated by the same two surgeons.
Anaesthesia (pentothal, succinylcholine, N_2O/O_2 in ratio 1/1, pancuronium, droperidol, halothane less than 0.5 %), postoperative management (nicomorphine at request of the patient, pain assessment

four days after the operation) and statistical analysis were the same as described in part I and II (Chapter 7 and 8) in detail. There are two differences:

- All patients received 10 mg diazepam orally and 0.5 mg atropine i.m. as a premedication one hour before surgery.
- In the IM group of the present (*second*) study, analgesia was provided with epidural bupivacaine (Marcaine®) 0.5% or 0.25% with adrenaline 1:200,000 in doses of 6-12 ml (depending on age, weight and length) and the catheter was removed immediately after surgery. In the EPID group of the present study, analgesia was performed during the operation by intravenous nicomorphine 0.1 mg/kg.

The postoperative pain managements of the IM and EPID groups were equal to those of the corresponding groups in the *first study* (Chapter 7).

Arterial blood samples for analysis of P_aCO_2 (5 times a day at fixed times) and X-rays of the thorax (preoperatively, postoperatively once every day) were taken at the same times as described in part II (Chapter 8) in detail.

Assessment of drowsiness took place on day 2 to avoid the influence of drugs given for premedication and anaesthesia (see Chapter 8).

The definitions of the words cardiac arrythmias, atelectasis and pneumonia, as used in this study, are given.

Cardiac arrythmias have been defined as those arrythmias not observed before operation.

Atelectasis is a word derived from Greek and could be translated by imperfect expansion. Atelectasis can be defined according to pathological anatomical (Anderson, 1977, chapter 26) and radiological criteria (Heitzman, 1984, chapter 12). A pathologist distincts atelectasis and collapse as two different items. Atelectasis meaning incomplete expansion of the newborn infant's lung and collapse meaning reduction in lung size due to loss of air. Our pulmonologist diagnosed atelectasis as loss of volume on X-ray (A-P direction, in bed). Bronchoscopic tracheo-bronchial toilet (BTT) was performed in all cases, if

atelectasis of a lobe or whole lung was present. If less than one lobe was involved, the clinical picture was descisive whether or not BTT was performed.

Pneumonia has been defined as the clinical feature of lung infection with infiltrative signs on the X-ray, positive sputum cultures accompanied by fever.

9.3 Results

1. Demographic data.

Age. The characteristics of the two analgesia groups of patients subdivided into three surgery groups are listed in Table 2. There is a significant difference in age for group II as compared with group I and III (ANOVA $p < 0.001$).

Table 2: Age.

Ages (years) in the various operation groups, average values with standard deviations in parentheses.

group	IM	EPID
I	57(13)	54(16)
II	20(10	18(08)
III	46(14)	42(26)

ANOVA	Main effect IM/EPID groups	p = 0.335
ANOVA	Main effect I/II/II groups	p = 0.000
ANOVA	Main effect COPD/noCOPD	p = 0.771

IM = intramuscular; EPID = epidural.
COPD = chronic obstructive pulmonary disease.

There is no significant difference in age between IM and EPID group, nor between COPD and noCOPD patients.

Sex. From Table 3, it follows that in this study there were more men than women. There was no significant difference in sex

Table 3: Sex.

Group size and distribution of sexes over the various groups.

	IM			EPID			
Group	Total	Female	Male	Total	Female	Male	FE-test*
I	44	11	33	24	6	28	ns
II	24	6	18	19	3	16	ns
III	3	1	2	5	2	3	ns
Total	71	18	53	58	11	47	ns

*) Fisher's exact test for significant difference of sex-distribution between IM/EPID groups.
IM = intramuscular; EPID = epidural.
ns = not siginificant.

distribution between the various groups.

Weight. In Table 4, the mean weights of patients in the six sub-groups are listed. Clearly, there is a correlation between age (Table 1) and weight (Table 4).

Table 4: Weight.

Average values and standard deviations (within parentheses) of weights (kg) in the various groups.

Group	IM	EPID
I	70(12)	71(10)
II	58(11)	64(11)
III	57(3)	52(11)

IM = intramuscular; EPID = epidural.

The presence of obesity was expressed in a weight/length ratio, defined as:

$$\text{(weight in kg)/(length in cm - 100)}.$$

If there is any overweight, this ratio will be greater than 1.1 (Bromage, 1978). Obesity implies a higher risk that postoperative

pulmonary complications may develop (Harman, 1979). There was a significant difference in the weight/length ratio between the various surgical groups. The weight/length ratio in group II and the EPID group III were less than in the others (ANOVA $p < 0.001$, Table 5). COPD patients in this study had no significant overweight.

Table 5: Weight/length ratio.

Average values of the weight/length ratio (kg/cm), as defined in the text, and their standard deviations (within parentheses) in the various groups.

	IM	EPID
I	0.97(0.15)	0.98(0.16)
II	0.77(0.08)	0.81(0.09)
III	0.90(0.09)	0.76(0.12)

ANOVA	Main effect IM/EPID groups	p = 0.609
ANOVA	Main effect I/II/II groups	p = 0.000
ANOVA	Main effect COPD/noCOPD	p = 0.434

IM = intramuscular; EPID = epidural.
COPD = chronic obstructive pulmonary disease.

2. The thoracic epidural catheter technique and its sequelae.

One hundred and twenty-nine patients received an epidural catheter at the T3-T4 level. In three patients it was impossible for us to insert the epidural catheter (these patients were excluded from the study). For the 71 patients in the IM group the catheter was removed after the operation. One spinal tap occurred in a patient with severe deformities of the thoracic curvature. The hanging drop test was positive in 98% of the cases.

Vasopressors were given if there was a decrease of systolic arterial blood pressure of more than 25% of the preoperative value. In 11%, a vasopressor (ephedrine sulfas) was needed after the administration of bupivacaine 0.5% with adrenaline, 1:200,000. No continuous infusion of dopamine nor of dobutamine was necessary, and no

inadvertent intravascular injection of the local anaesthetic occurred.

3. Postoperative pain.

Table 6 shows the results of pain assessment by the patient on the fourth day after operation. In this study the EPID group assessed their pain relief significantly better than the IM group (χ^2-test, $p = 0.007$). More than 57% of the patients in the EPID group assessed their pain as pain-free and no patient experienced severe pain. In the IM group 31% of the patients assessed their pain as pain-free and 4 patients experienced severe pain.

Table 6: Pain assessment by the patient.

Postoperative pain assessment 4 days after surgery by the patient. Frequencies of scores in the 63 intramuscular (IM) and 56 epidural (EPID) patients. (χ^2-test, $p = 0.007$).

Score/group	IM	EPID
Pain free	19	32
Slight pain	23	17
Moderate pain	17	7
Severe pain	4	0

In Table 7 the pain relief assessment by the medical team is listed. In the EPID-group 60% of the patients were judged to have had excellent pain relief compared to 17% in the IM group, being a significant difference (χ^2-test, $p < 0.001$). Unsatisfactory pain relief was observed in 11 patients in the IM group compared to none in the EPID group.

The onset of pain relief by nicomorphine was also studied in the two groups. At times 0, 5, 15, and 30 minutes after the administration of nicomorphine along either route, patients evaluated their discomfort as mild, moderate or severe. The

Table 7: Pain assessment by the medical team.

Postoperative pain assessment 4 days after surgery by the team. Frequencies of scores in the 64 intramuscular (IM) and 57 epidural (EPID) patients. (χ^2-*test*, $p < 0.001$).

Score/group	IM	EPID
Excellent	11	34
Sufficient	42	23
Unsatisfactory	11	0

development of pain relief obtained in this way is depicted in figure 9.1. Fifteen minutes after the administration of nicomorphine 62% of the patients in the EPID group experienced nil/mild discomfort against 37% in the IM group.

4. Nicomorphine requirements.

Nicomorphine requirements on day 1,2,3, and the total amount required are shown in figure 9.2. Significant differences in nicomorphine requirements between the analgesia groups (EPID/IM) were found on all three days. The highest nicomorphine requirement was on day 2, in all surgical groups. In the EPID group the requirements of nicomorphine over a period of three days were 42 mg (sd = 18) versus 92 mg (sd = 33) in the IM group.

5. Pre- and postoperative $PaCO_2$.

Average values of $\Delta PaCO_2$, defined as the highest $PaCO_2$ of the patient on day 1, 2 or 3 minus his (her) preoperative value of $PaCO_2$ are shown in figure 9.3. The EPID group ventilated significantly better on day 2 (ANOVA, $p = 0.05$). Between surgery groups (I,II,III) there is no difference in $\Delta PaCO_2$ on any day. In surgery group II the IM group ventilated better than the EPID group on all three days, though differences were not significant. Not that surgery group III consists of only 8 patients.

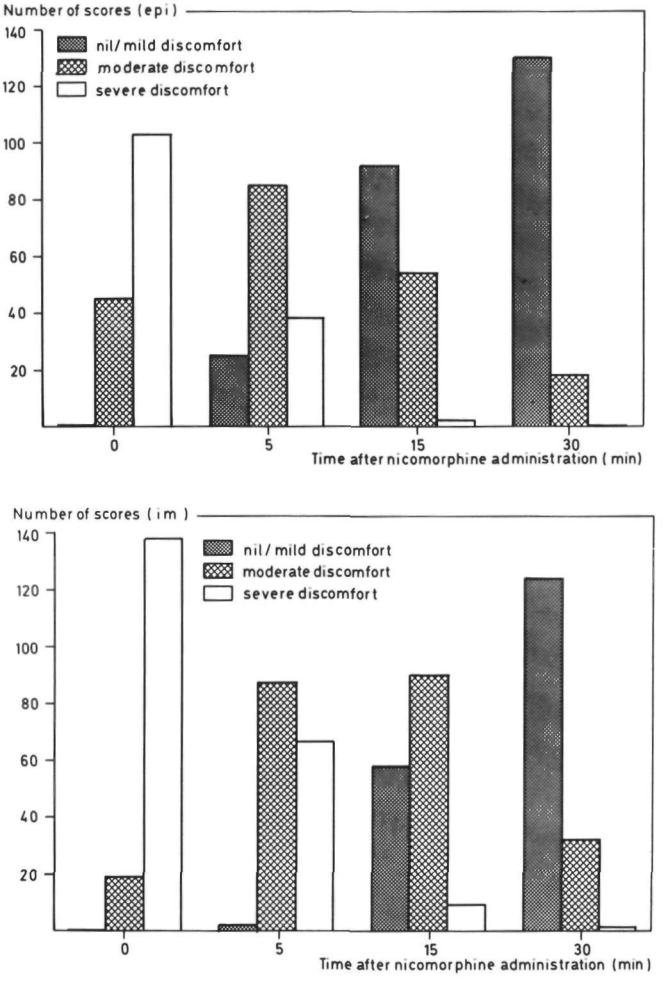

FIG. (9.1) *The onset of the analgesic effect of nicomorphine. Histograms of pain scores at 0, 5, 15, and 30 minutes after administration of nicomorphine in the epidural group (EPID, top, total of 148 scores in 58 patients) as well as the intramuscular group (IM, bottom, total of 157 scores in 71 patients). Note that a single patient possibly supplies more than one evaluation point, because pain assesment was carried out several times.*

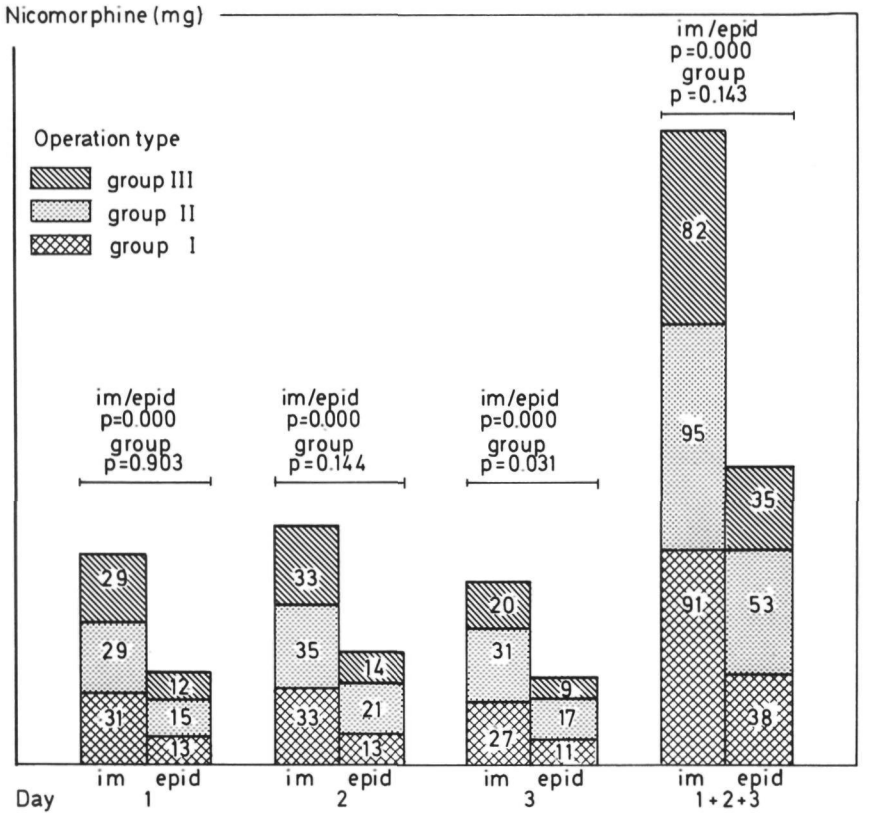

FIG. (9.2) *Nicomorphine dose requirements of the intramuscular (IM) and epidural (EPID) group in the various surgical groups (I, II and III) on day 1, 2 and 3 and the sum of nicomorphine requirements over these three postoperative days. Statistical analysis by ANOVA (n = 129). The amount of nicomorphine required in each sub-group is indicated by figures in the squares. Significances (p-values) are indicated at the top of the figure for comparison between analgesia groups (im/epid) and surgical groups (I, II and III).*

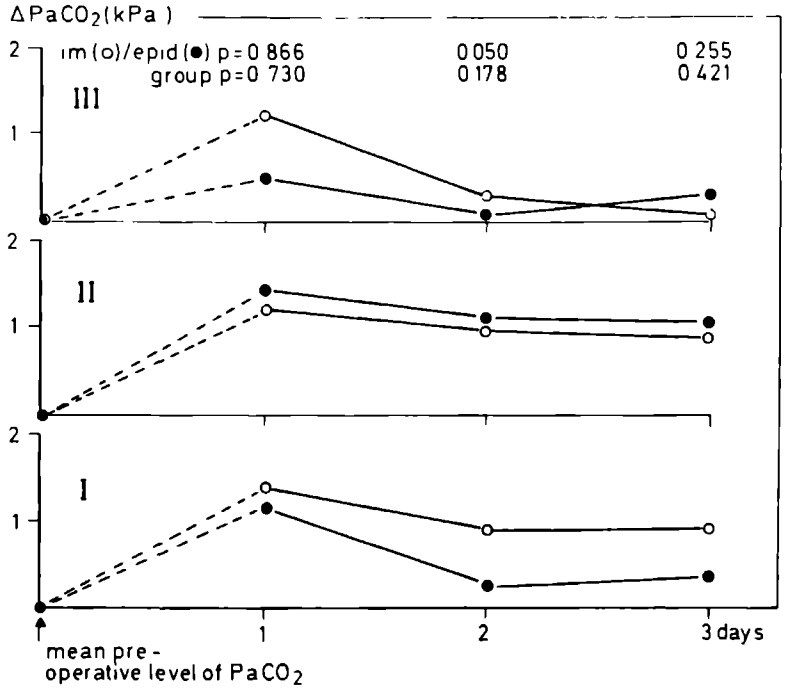

FIG. (9.3) *Average values of ΔP_aCO_2 (kPa) in the various surgical groups (I, II and III). ΔP_aCO_2 is defined as the highest P_aCO_2 of the patient on day 1, 2 or 3 minus his/her preoperative value. Statistical analysis by ANOVA (n = 129). The average standard deviation over all data-points amounted to 0.65 kPa. Significances (p-values) are indicated at the top for comparison of analgesia groups (im/epid) and surgical groups (I,II,III). The EPID group ventilated significantly better on day 2 (ANOVA, p = 0.05).*

6. The postoperative complications of surgery

Atelectasis. The number of radiologically verified atelectases on the first 3 days postoperatively in the three surgical groups in total and subdivided in COPD and non-COPD patients are depicted in figure 9.4.

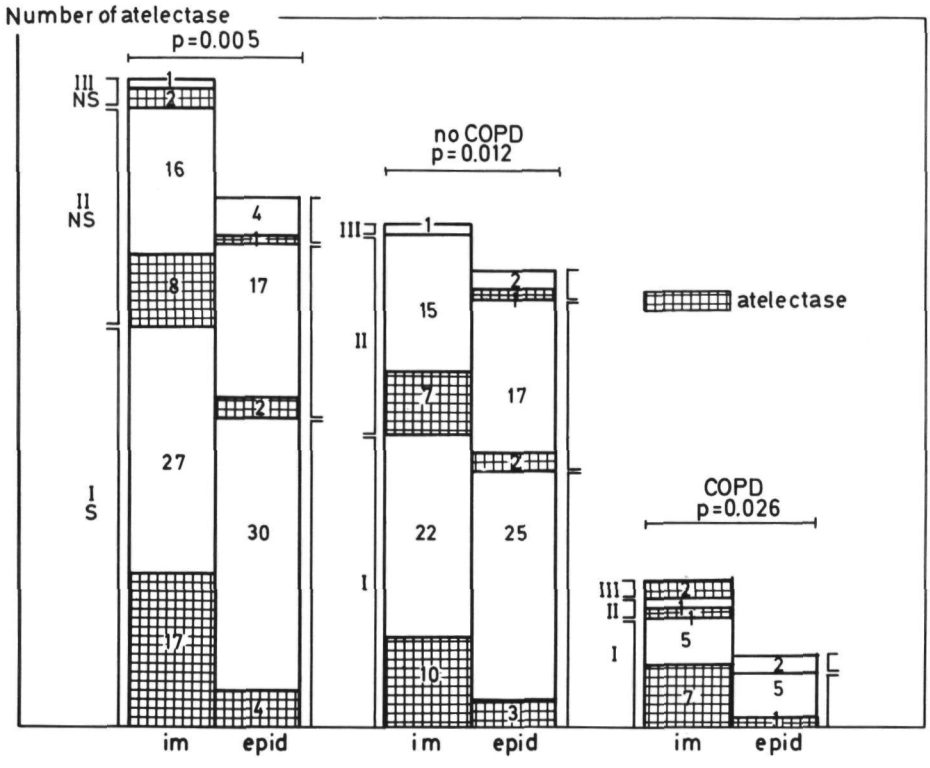

FIG. (9.4) *Histograms of the total number of atelectases on the first 3 postoperative days in the various surgical groups (I,II,II). The numbers of patients are also indicated by figures in the histogram. The total number of patients is then subdivided in patients with and without chronic obstructive pulmonary disease (COPD). Statistical analysis by Fisher's exact test.*

If a patient developed several atelectases at different times, it was considered as a single count in the statistical analysis. The number of atelectases in the EPID group (7) was significantly lower than in the IM group (27, FET, p = 0.005). Most of the atelectases developed for the IM group as well as for the EPID group on day 2. In the EPID group no single atelectasis developed on the third

postoperative day, in contrast with the IM group, in which 9 atelectases occurred on that day.
Unintentianally, the IM group contained more patients with COPD than the EPID-group did. (figure 9.5).

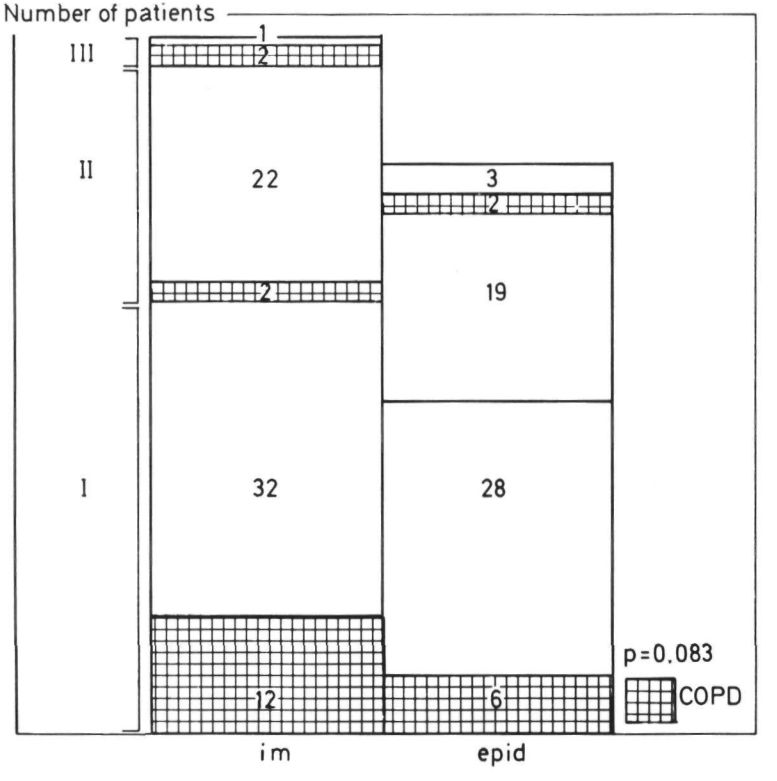

FIG. (9.5) *Distribution of COPD patients over the various groups. The number of patients (COPD and non-COPD) in the various analgesia and surgical groups are indicated by figures in the histogram.*

BTT. The number of BTT's performed by our pulmonologist, in total and again subdivided into patients with and without COPD, is depicted in figure 9.6. The statistical analysis (FET, p = 0.06) is again in favour to the EPID group (5 BTT's) compared to the IM group (13 BTT's).

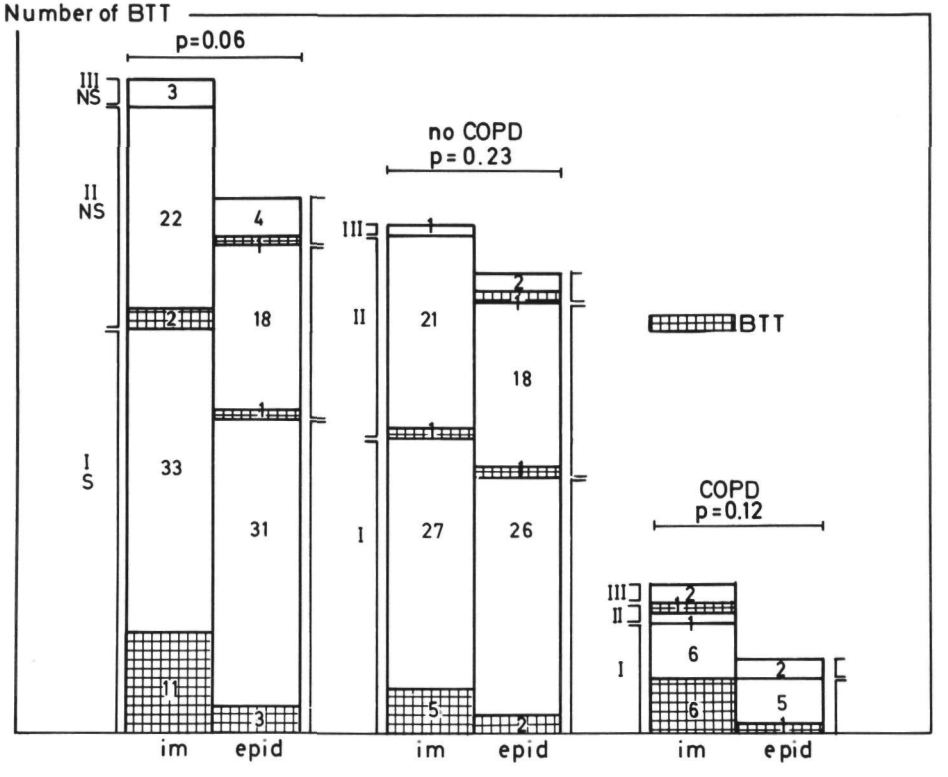

FIG. (9.6) *Histogram of bronchoscopial tracheobronchial toilets (BTT) performed on the first 3 days in the various surgery groups (I,II,III). The frequencies are also indicated by figures. The total number of patients is then subdivided in patients with and without chronic obstructive pulmonary disease (COPD). Statistical analysis by Fisher's exact test (s: $p < 0.05$, ns: $p > 0.05$).*

7. Complications due to general effects of opiates.

Drowsiness. In Table 8 is shown that significantly more patients were markedly drowsy after administration of i.m. nicomorphine (FET, $p = 0.003$).

Table 8: Drowsiness.

General complications of opiates: drowsiness. Number of drowsy patients in the IM and EPID groups. (FE-test, $p = 0.003$).

	IM	EPID
No drowsiness	32	45
Markedly drowsy	28	13

IM = intramuscular; EPID = epidural.

Other complications. Other complications, as bradycardia, hypotension, slow respiratory rate, nausea, vomiting, itching and urinary retention, are listed in Table 9. No significant differences in other complications were found after administration of nicomorphine between both analgesia groups.

8. Cardiac arrythmias.

There were no significant differences in this respect between patients of IM and EPID-group. Most cardiac arrythmias occurred in surgical group I. Of the patients who were using cardiac drugs before operation 50% developed cardiac arrythmias after the operation. Of those patients who did not use cardiac drugs before the operations only 14% developed cardiac arrythmias after surgery.

Table 9: Other complications than drowsiness.

Incidence of complications due to general effect of opiates (other than drowsiness) in the IM and EPID anaesthesia groups (n is number of cases studied for each item).

	IM		EPID		FE-Test
	n	Compl	n	Compl	p/sign
Heart rate < 60 beats/min	68	0	58	0	ns
Mean arterial press. drop > 20%	68	0	58	1	ns
Respiratory rate < 14/min	68	4	58	2	ns
Nausea	58	6	67	5	ns
Vomiting	58	6	67	2	ns
Itching	63	1	55	1	ns
Urinary retention	60	38	51	35	0.135 (ns)

IM = intramuscular; EPID = epidural.
Statistics by Fisher's exact test.

9.4 Discussion

In this discussion we will compare the four analgesia groups as described in table 1.

Demographic data. In the *first study* the patients in the EPID-group were older than the patients in the IM group, in the *second study* there was no significant difference in age. In the COPD patients of the *first study* there was in contrast to the *second study* significant overweight.

Epidural catheter technique and its sequelae. In both studies (212 patients received an epidural catheter) only two spinal taps occurred, although most of the catheters were inserted by (supervised) residents. In only three patients it was impossible to identify the epidural space at the T3-4 level. A preferential downward spread of the local anaesthetic solutions was observed in both studies (The block was tested after the initial test dose as well as after the final dose.) which may be due to the increased volume of the epidural space from cranial to caudal.

Postoperative pain. In the *first study* the pain assessment was introduced into the protocol at a later stage, so that statistical analysis was inappropriate. In the *second study* with the same postoperative analgesia as in the *first study*, the EPID group scores significantly better than the IM group. For the same reasons as in the *first study* the scores are negatively influenced by surgical Group II. Both groups (IM and EPID) provided in both studies effective analgesia of a rapid onset.

Nicomorphine requirements. The nicomorphine requirements were highest in the IM group, which received during the operation epidural bupivacaine 0.5% with adrenaline 1:200,000 (92 mg, sd = 33). When the epidural block weares off, many painful stimuli are transmitted to the central nervous system. By giving analgesics intramuscularly it is often impossible to have enough opiate receptors occupied to provide good analgesia because of the slow absorption from the i.m. absorption sites. (Naturally, even intramuscularly, it is always possible the occupy all receptors by increasing the dose.) This will only be observed after painful operations.

In both studies patients in the EPID-group required significantly less nicomorphine (29 mg, sd = 10; 42 mg, sd = 18) for effective pain relief over a period of 3 days compared to the IM group (52 mg, sd = 30; 92 mg, sd = 33). Moreover, the postoperative amount of nicomorphine required in the EPID group (group 2 in table 1) receiving bupivacaine epidurally during the operation (29 mg, sd = 10) was significantly less than in the EPID group (group 3 in table 1) receiving nicomorphine i.v. during the operation (49 mg, sd = 18).

Pre- and postoperative P_aCO_2. In the *second study* six patients showed respiratory rate below 14 /min (3 in the EPID-group, 3 in the IM group). None of the patients had a P_aCO_2 of more than 7.2 kPa at any time. As has been noticed in the *first study* the low breathing frequency indicates rather the painless and deep

breathing than a ventilatory depression.

We also analysed the effects on ΔP_aCO_2 of bupivacaine epidurally or nicomorphine i.v. during operation, on the various days in all patients (both studies). Patients receiving epidural bupivacaine peroperatively ventilated on day 1 significantly better than patients receiving nicomorphine (ANOVA, p =0.014). The effects of nicomorphine epidurally or i.m. postoperatively on ΔP_aCO_2 were analysed as well. Patients receiving nicomorphine epidurally ventilated significantly better on all three days (ANOVA, day 1 p = 0.006, day 2 p = 0.009, day 3 p = 0.017).

The postoperative pulmonary complications of surgery. The EPID group of patients in the *first* and *second study* have less pulmonary complications. There is no significant difference in complications whether the analgesia during the operations was provided by epidural bupivacaine 0.5% with adrenaline 1:200,000 or by nicomorphine i.v.. However, the amount of nicomorphine necessary to provide effective analgesia was less in the group receiving bupivacaine during the operation and this is one of the reasons we prefer the combination of bupivacaine by epidural catheter during the operation followed by nicomorphine through the epidural catheter postoperatively.

In the *first study* only one 7-year-old girl of surgery group II developed a pneumonia on the third postoperative day, in the *second study* a 10-year old girl of group II developed pneumonia again on the third postoperative day.

In the *first study* none of the patients in either analgesia group, needed to be ventilated postoperatively. In the *second study* four patients were ventilated postoperatively. Because of surgical complications and subsequent prolonged duration of anaesthesia it was considered desirable to ventilate the patients prophylacticly. The data of these patients were not included in this analysis.

In the *first* as well as the *second study* one patient died directly after surgery. Autopsy to investigate the exact cause of death was not permitted.

Complications due to the general effects of opiates. Less drowsiness as occurs after the epidural administration of nicomorphine in both EPID-groups is advantageous for thoracic operations.

Postoperative nausea and vomiting occur in about one third of the patients, the incidence of which varies with the anaesthetic used, but none is entirely free of these sequelae (Gray, 1980, chapter 54). Our figures regarding nausea and vomiting include the direct postoperative occurence of these sequelae, and are not always directly related to the nicomorphine administered.

The incidence of urinary retention is very high in both the IM and EPID-group in the *second study*. In the *first study* urinary retention was significantly higher in the EPID group. Most patients undergoing a pneumectomy received a urine catheter for monitoring urine output. Patients from surgical group II stayed in supine position during the first five postoperative days. If both groups of patients are excluded, then there was significantly less urinary retention in patients not receiving any epidural drug (IM group of *first study*, χ^2-test, $p = 0.05$). The epidural administration of drugs (however, at thoracic level) apparantly induces urinary retention. Naloxone may be the drug of choice for reversal of the (nico)morphine-induced urinary retention (Husted, 1985). However, in stead of using this drug, patients received a urinary catheter.

Cardiac arrythmias. Most of the arrythmias observed were atrial fibrillation, atrial flutter and ventricular extra systoles. The incidence of arrythmias in the *second study* (50% of the patients using cardiac drugs and 14% of the patients not using cardiac drugs) is lower than in the *first study* (68% resp. 38%). To the high incidence contributes, that transient arrythmias were included in this study.

Pulmonary function tests. From the 281 patients involved in the *first* and *second study*, the pulmonary function tests of 230 patients were analysed (Some data were either not available or incomplete). The normal values of these tests were derived from the European Coal and Steel Community The pulmonary function tests shown in Table 10 are the figures after optimal treatment by the pulmonologist

In the integral study no significant differences in pulmonary function tests, related to the individual normal values, were observed between patients with and without atelectasis According to literature (Margand, 1981) a decreased forced expiratory volume in 1 second, enlarges the risk of postoperative pulmonary complications. This is not demonstrated by our results. The lack of correlation in this study may be related to the excellent preoperative treatment by the pulmonologist. These conclusions are not affected by the exclusion of surgical group II from the analysis

Comparison of the test values, related to the individual normal values, of COPD versus non-COPD patients, show significant differences for functional residual capacity and the forced expiratory volume in 1 second only (ANOVA, $p < 0.05$.)

Table 10: Pulmonary function tests

Mean values of pulmonary function tests in the IM and EPID groups of the first and second study (n = 230) are listed. Some data were not available or incomplete. Standard deviations in parentheses. TC =total capacity, VC = vital capacity, RV = residual volume, FRC = functional residual capacity, FEV1 = forced expiratory volume in 1 second, The ratios VC/TC (%), FEV1/VC (%), FRC/TC (%), RV/TC (%) are listed, and subdivided into patients groups for atelectasis (Atel) and no-atelectasis (noAtel), COPD and noCOPD patients. Normal values are derived from the European Coal and Steel Community.

	First Study		Second Study	
Total n=230	IM, n=59	EPID, n=71	IM, n=59	EPID, n=41
Actual TC (%) Normal TC	88 (17)	92 (16)	97 (18)	98 (17)
TC(ml)	4790 (1664)	6139 (1510)	5932 (1463)	6191 (1307)
VC/TC(%)	69 (10)	66 (11)	71 (8)	66 (16)
Atel,noAtel	66(14),69(9)	64(11),66(11)	78(1),70(8)	64(10),66(18)
COPD,noCOPD	58(16),70(9)	58(15),69(7)	62(6),67(17)	59(8),72(8)
FEV1/VC (%)	74 (13)	68 (19)	71 (12)	76 (11)
Atel,noAtel	66(16),77(11)	64(20),69(19)	69(12),73(11)	79(9),75(11)
COPD,noCOPD	51(10),78(10)	47(18),77(10)	62(15),74(10)	58(10),77(9)
FRC/TC (%)	52 (9)	53 (10)	53 (8)	49 (7)
Atel,noAtel	52(9),51(9)	55(11),53(10)	54(7),53(9)	41(1),49(7)
COPD,noCOPD	69(11),49(6)	61(9),50(9)	58(7),52(8)	58(2),48(7)
RV/TC (%)	31 (10)	34 (11)	34 (15)	29 (8)
Atel,noAtel	34(14),31(9)	36(11),34(11)	36(10),34(18)	22(1),30(8)
COPD,noCOPD	42(16),30(9)	42(15),32(7)	38(6),33(17)	41(8),28(8)

In conclusion: the anaesthesia technique as used in the EPID group of the *first study*, balanced intravenous anaesthesia with high-thoracic epidural block during the operation as well as epidural nicomorphine postoperatively is strongly recommended for thoracic operations. Peroperative epidural bupivacaine improves cardiovascular stability (Hennek, 1984), diminishes the

postoperative epidural requirements of nicomorphine and postoperative epidural nicomorphine provides effective and rapid analgesia, improves ventilation and diminishes the number of postoperative pulmonary complications.

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CHAPTER 10

THE INFLUENCE OF HIGH-THORACIC EPIDURAL ANALGESIA ON THE CARDIOVASCULAR SYSTEM.

10.1 Introduction

Cardiovascular changes associated with high Thoracic Epidural Analgesia (TEA) have been investigated during the last 20 years, but still some controversy exists. Using mepivacaine (Scandicaine®), Otton (1966), McLean (1967) and Nishumura (1985) observed significant cardiovascular changes. However, Ottesen (1978) reported minor cardiovascular changes after high TEA. Also Sjögren, using lidocaine, found that high TEA influenced the cardiovascular system only slightly. In a clinical study we have observed major cardiovascular changes using mepivacaine for high TEA. After changing our practice and using bupivacaine, only minor cardiovascular changes occurred. Since no studies concerning the influence of high TEA using bupivacaine on the cardiovascular system were available the present study was undertaken.

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Submitted for publication.

10.2 Patients and methods

Patients were informed by the investigator and gave their consent for the study. The investigation was approved by the Ethical Committee of the University Lung Center, "Dekkerswald". The investigation comprised 10 patients: 5 without any cardiovascular disorder, and 5 with cardiovascular disease (table 1).
Patients were premedicated with diazepam (Valium®) 10 mg orally one hour before the investigation. An intravenous catheter (Abbocath 18 G) was placed and Ringer solution 100 ml/hr was infused. The left radial artery was cannulated with B-D-cath 20 G for blood pressure measurements and blood sampling. A 16 G Tuohy needle was inserted at T1-T2 level, while the patient was awake and sitting. The paramedian approach was used and the epidural space was identified with the hanging drop technique. The catheter (Braun) was directed cephalad and advanced 3-4 cm. The patient was then placed supine. A triple lumen Swan Ganz thermodilution catheter (American Edwards Laboratories) was inserted after local infiltration with plain lidocaine 1% (2 ml) to the pulmonary artery from the left subclavian vein (for left thoracotomy) or from the right subclavian vein (for right thoracotomy). The position of the Swan Ganz catheter was then controlled by an X-ray of the thorax (A-P direction).

Systemic and pulmonary arterial pressure, central venous pressure (CVP), pulmonary capillary wedge pressures (PCWP), ECG and heart rate (HR) were monitored on a Siemens monitor (Sirecust 404). The zero reference point for all pressure measurements was 5 cm dorsal to the sternal angle. Cardiac Output (CO) was determined by thermodilution, by the injection of 10 ml dextrose 5% at 0^{0} C. Thermodilution curves were computed on an American Edwards Laboratories Cardiac Output computer with corrections for variations of injected and body temperature.

After a resting period of 30 minutes, the cardiovascular parameters were measured (control study, CS). All measurements were done at the end of an expiration. Measured values were the average

Table 1: Results.

Measurements and calculations during the control period and after TEA. The recorded value for each parameter is an average of 5 observations at the end of expiration.

Patients with cardiovascular disease.

N[1]	A	BSA		HR	PCWP	CVP	MAP	CI	SVI	SVR	PVR	LVSWI	RVSWI
1[2]	72	1.75	CS	55	1	0	65	2.4	43.6	1220	225	37.9	7.8
			TE	58	5	0	71	2.6	44.8	1240	192	40.2	9.8
2[3]	76	1.96	CS	56	2	1	130	2.0	35.7	2580	80	62.1	3.0
			TE	54	5	1	118	2.0	37.0	2400	62	56.9	4.0
3[4]	51	1.96	CS	65	2	0	92	2.6	40.0	1098	78	49.0	3.8
			TE	67	3	1	74	2.3	34.3	1298	53	33.1	2.8
4[5]	71	1.57	CS	67	3	3	86	3.3	49.3	1267	137	55.6	8.1
			TE	64	4	3	101	3.2	50.0	1546	189	66.0	11.0
5[6]	62	1.82	CS	79	6	3	81	3.4	43.0	1008	142	43.9	10.0
			TE	73	4	1	75	3.3	45.2	975	132	43.6	8.7
mean	67	1.81	CS	64	2.8	1.4	91	2.7	42.3	1435	132	49.7	6.5
sd		0.16		10	1.9	1.5	24	0.6	5.0	648	60	9.5	3.0
mean			TE	63	4.2	1.2	88	2.7	42.3	1492	126	48.0	7.3
sd				7	0.8	1.1	21	0.6	6.4	547	67	13.3	3.6

Patients without cardiovascular disorder.

6	40	1.77	CS	80	13	10	104	5.0	62.5	842	63	77.4	14.6
			TE	87	13	11	98	5.8	66.7	680	39	77.1	12.6
7	57	1.82	CS	87	12	1	100	3.8	43.7	1151	35	52.3	7.7
			TE	87	8	1	87	4.5	51.7	840	20	55.5	7.0
8	55	1.50	CS	63	8	4	107	3.3	52.4	1682	82	70.6	9.6
			TE	56	7	2	100	2.7	48.2	1898	116	61.0	8.7
9	78	1.96	CS	71	1	1	95	2.8	39.4	1350	72	50.4	3.3
			TE	67	4	1	94	3.2	47.8	1181	76	58.5	6.5
10	24	1.84	CS	62	11	10	91	2.3	37.1	1525	56	40.4	7.1
			TE	57	10	10	90	2.4	42.1	1451	54	45.8	7.4
mean	51	1.78	CS	73	9	5.2	99	3.4	47.0	1310	62	58.2	8.5
sd		0.17		11	5	4.5	7	1.0	10.4	328	18	15.3	4.1
mean			TE	71	8	5.0	94	3.7	51.3	1210	61	59.6	8.4
sd				15	3	5.0	5	1.4	9.3	487	37	11.4	2.5

[1]) key: N patient number, A age in years, BSA body surface area (m^2), HR to RVSI are defined in the text (calculations).
[2]) Angina Pectoris (AP) II NYHA, using β-adrenoceptor antagonist and digoxine (Lanoxin®).
[3]) Hypertension using β-adrenoceptor antagonist.
[4]) Preveous Coronary Bypass.
[5]) AP II NYHA, using digoxine and isosorbidedinitrate (Cedocard®)
[6]) Myocardial Infarction 1984, using digoxine and β-adrenoceptor antagonist.

CS = Control study
TE = Thoracic Epidural Analgesia study
SD = Standard deviation

of 5 observations. The standard deviation of the 5 determinations was 0.31 ℓ min^{-1} before and 0.25 ℓ min^{-1} after injection of the local anaesthetic. After these control measurements TEA was induced by injection of 4-6 ml plain bupivacaine 0.5% solution into the epidural catheter. No test dose was given.

The distribution of sensory loss, 20 minutes later, was determined by pin-prick at both sides. Thirty minutes after the injection of the local anaesthetic, all the cardiovascular parameters were measured again (TEA study) (figure 10.1).

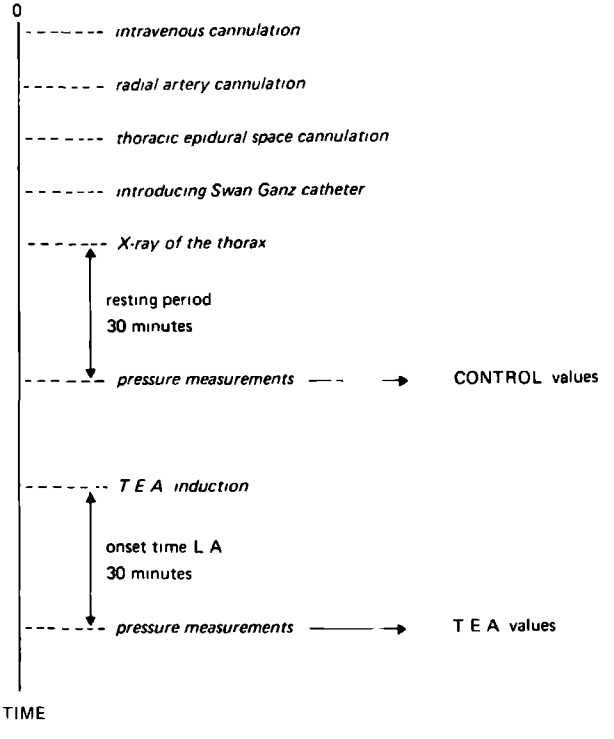

FIG. (10.1) *The course of the investigation, divided into a control study and a Thoracic Epidural Analgesia study.*

Calculations

For the calculations we used the Epson HX-20 computer.

CI	= CO/BSA	: $\ell\ min^{-1}m^{-2}$
SVI	= (CI/HR) x 1000	: $ml\ beat^{-1}m^{-2}$
LVSWI	= (MAP - PCWP) x SVI x 0.0136	: $gm\ m\ m^{-2}beat^{-1}$
RVSWI	= (13.6 x CO x MPAP)/(HR x BSA)	: $gm\ m\ m^{-2}beat^{-1}$
SVR	= (MAP - CVP) x 80/CO	: $dyn.sec.cm^{-5}$
PVR	= (MPAP - PCWP) x 80/CO	: $dyn.sec.cm^{-5}$

Where:

CI	= Cardiac Index
CO	= Cardiac Output
BSA	= Body Surface Area
SVI	= Stroke Volume Index
LVSWI	= Left Ventricular Stroke Work Index
RVSWI	= Right Ventricular Stroke Work Index
PCWP	= Pulmonary Capillary Wedge Pressure
MPAP	= Mean Pulmonary Arterial Pressure
SVR	= Systemic Vascular Resistance
PVR	= Pulmonary Vascular Resistance

Statistical analysis

Statistical analysis was performed by Student's t-test for unpaired data (comparison between cardial disabled and fit patients) or paired data (comparison of situations before and after installation of epidural analgesia).

10.3 Results

Table 1 shows the results of measurements and calculations of the control and TEA studies in all patients. The amount of local anaesthetic used was dependent on the body weight and the length of the patient. The mean amount used was 4.4 ml. (range 4 to 6 ml). TEA induced sensory loss was tested at both sides and showed a rostral border at C7 (range C6 to T1) and a caudal border at T5 (range T4 to T6). Two patients developed motor blockade of the hand musculature. TEA did not result in a significant change of any of the cardiovascular parameters measured, when compared to the values obtained in the control study.

In patient 1, TEA resulted in a slight increase in PCWP, CI and MAP. In all patients with cardiovascular disorders, PCWP increased slightly, except in patient 5. In patient 9 without any cardiovascular disorder, PCWP increased also slightly. We did not notice important increase of CVP in any patient. For the high CVP, PCWP, MAP and CI preoperatively in patient 6, stress is a possible explanation. The high CVP in patient 10 was caused by a massive benign tumor compressing the right atrium. Only in one patient (patient 8, without any cardiovascular disorder) we noticed an important decrease in CI (22%) and in HR (11%).

10.4 Discussion

TEA is often used during and after thoracic and upper abdominal surgery, but also after chest injuries. High TEA (T1-T5) will block the sympathetic innervation of the heart: the maximal depression of contractility and decrease in blood pressure may be expected when the upper two thoracic segments become involved, especially at the left side (Bromage, 1978, chapter 10).

The distribution of sensory loss was determined by the pin prick method. However, there is no point in testing for blockade of T1-T2 by testing above the nipple line, since this area has double

innervation from T1-T2 and C3-C4, so that normal sensation remains even when T1 and T2 are blocked. Thus, residual activity in the sensory dermatomes T1 and T2 is checked by testing skin sensation on the inside of the arm above the elbow (T2) and below the elbow (T1). Residual motor activity in T1 can also be checked by testing the ability of the patient to hold a sheet of paper between the stretched out fingers (interossei muscles, innervated by C8-T1) (Cousins, 1980, chapter 8).

Recorded values of HR, CVP and PCWP continuously changed with the respiratory cycle, especially during spontaneous breathing. Therefore we recorded these values at the end of the expiration. Even then, these values varied from beat to beat, but less than during the respiratory cycle. For this reason we averaged five end-expiratory values.

After high TEA with plain mepivacaine 1% at level C7-T1, Otton (1966) and McLean (1967) reported a significant reduction in HR and CI, constant the SVI and a rise in CVP. However, the average rise (though statistically significant) in CVP in both studies of 1.5 mm Hg, is the normal variation within an individual, also without TEA. The mean reduction in HR of 13 beats/min (Otton, 1966) and 7 beats/min (McLean, 1967) is consistantly occurring in every patient. The values for Otton's parameters were an average of duplicate readings, but Otton as well as McLean did not describe, in particular for the CVP, and HR, at which point of the respiratory cycle they recorded their values. Besides, a beat to beat variation in HR of at least 5-10% has to be taken into account.

Nishumura (1985) investigated the influence of TEA at level T6-T8 with plain mepivacaine 2% on the cardiovascular system. From their study they reported a decrease in MAP, CI and HR, but in contrast to Otton and McLean they also observed a decrease in MPAP, PCWP and CVP. The local anaesthetic dose used, however, was twice as much as the dose Otton and McLean used. Nishumura also did not describe exactly the extent of the epidural block (table 2).

Table 2· Influence of TEA.

Influence of TEA on cardiovascular system. Data from six studies.

Ref	Pat	level TEA	LA	conc (%)	vol (ml)	amount (mg)	ext. block	HR	MAP	CI	CVP	PCWP
(1)	6 fit	C7-T1	plain mepi	1%	7	70	>T4	↓*	↓	↓*	↑*	-
(2)	7 fit	C7-T1	plain mepi	1%	7	70	>T4	↓*	↓	↓*	↑*	-
(4)	10 fit	T4-5/T5-6	plain mepi	2%	5	100	C7-T6	↑*	=	=	=	=
(3)	37 clin	T6-7-8	plain mepi	2%	8	160	>T4	↓*	↓*	↓*	↓*	↓*
(5)	23 fit	T5-6	plain ligno	2%	8	160	T1-2/T12	=	↓*	=	=	=
H/L	5 fit+ 5 card dis	T1-2	plain bupi	0.5%	4.5	22.5	C7-T4	=	=	=	=	=

Ref = reference number; H/L = Hasenbos and Liem (present study), Pat = type of patient, fit = fit patients, clin = clinical patients; card.dis = patients with cardial disorder, LA = Local Anesthetic; mepi = mepivacaine, ligno = lignocaine, bupi = bupivacaine, ↓ = decrease; ↑ = increase, = = no change; - = not measured, * = significant ($p < 0.05$).

Sjogren and Wright (1972) used plain lidocaine 2% for the induction of TEA at level T5-T6. They concluded from their study, that TEA influenced central and peripheral circulation only slightly.

None of the authors mentioned before, described at which point of the respiratory cycle they recorded their cardiovascular parameters.

Using mepivacaine for high TEA, we also noticed significant cardiovascular changes, especially in patients with cardiovascular disorder. Favourable results with the use of bupivacaine in clinical practice are reported (Hennek, 1984; Chapter 7). TEA with bupivacaine did not decrease HR, during operation, MAP showed no peak levels in response to the surgical trauma (Hennek, 1984). The reason for the difference in cardiovascular changes between mepivacaine and bupivacaine may be due to the specific autonomic system saving effect of bupivacaine in comparison to other local anaesthetics (Sheskey, 1982). Bupivacaine has a higher pKa (8.1) in comparison to mepivacaine (7.6) and thus a smaller fraction of its lipid soluble non ionized form is present at physiological pH. This

explains its poor ability to penetrate the afferent and efferent nerve fibers to the heart (T1 to T4-T5).

Lidocaine has also a higher pKa (7.9) in comparison to mepivacaine. Besides, intravenously infused lidocaine (with low arterial plasma concentrations of about 4-8 µg/ml.) has effects on the central circulation as shown by increased CO, MAP and HR (Sjögren, 1972).

In patients using β-adrenoceptor antagonists, TEA may have additive, depressive effects on SA and AV nodal functions, as well as on the left ventricular inotropy (Hotvedt, 1984). However, in this study and in more than 300 patients in whom we performed TEA with bupivacaine (several patients were using β-adrenoceptor antagonists) we did not encounter significant cardiovascular changes (Chapter 7).

In conclusion: high TEA with bupivacaine produces only minor cardiovascular changes, not only in healthy patients but also in clinical patients with cardiovascular disease.

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CHAPTER 11

THE INFLUENCE OF NICOMORPHINE ADMINISTERED INTRAMUSCULARLY VERSUS HIGH-THORACIC EPIDURALLY ON THE RESPIRATORY SYSTEM.

11.1 Introduction

It is of main interest that, since the introduction of nicomorphine as an analgesic, no reports of ventilatory depression by epidural administration of this drug have been reported (Pinckaers, 1982; Dirksen, 1984; Chapters 7 and 8). A number of clinical studies on epidural morphine and diamorphine have been published (Doblar, 1982; Gustafsson, 1982; McCaughey, 1982; Kafer, 1983; Malins, 1984). Our experience (Chapter 7) with postoperative epidural administration of nicomorphine in which no ventilatory depression was observed, despite of the high position of the epidural catheter, stimulated us to quantify this observation.

In this study we investigated two patient groups; one receiving nicomorphine for postoperative pain relief by intramuscular application, the other by high thoracic epidural administration in doses for which the visual analogue scale (VAS) pain scores in both groups responded comparably.
In all patients the effects of nicomorphine administration on the ventilatory and mouth occlusion pressure CO_2-response were measured and the two groups were compared.

M. Hasenbos and M. Simon, J. van Egmond, H. Folgering, P. van Hoorn. "*Postoperative analgesia by nicomorphine, intramuscular versus high-thoracic epidural administration. Effect on ventilatory and airway occlusion pressure response to CO_2.*" (Act. Anaesth. Scand., in press).

11.2 Patients and methods

Patients

Two groups of patients scheduled for thoracic surgery were studied. All patients gave informed consent. The thoracic operations comprised either thoracotomy with pulmonary surgery or a thoracic wall correction of a pectus excavatum or pectus carinatum. Patients were allocated randomly to postoperative intramuscular nicomorphine administration (IM-group) or to postoperative epidural nicomorphine administration (EPID-group). This study comprises twenty-four patients, 10 in the IM-group and 14 in the EPID-group. In patients of the EPID-group an epidural catheter was placed at T2-T3 or T3-T4 level before operation. The characteristics of the two patient groups are listed in table 1. The incidence of thoracic wall corrections in the EPID-group is unintentionally higher than in the IM-group. This is also the explanation of the difference (though statistically not yet significant, $p = 0.06$ in a t-test) in age between the two groups, since thoracic wall corrections are mostly performed in young patients.

Table 1: Patient group characteristics.

Sex, age (years, average values with standard deviations in parentheses) and distribution of surgery types.

	Total	Male	Female	Age Mean (SD)	Thoracic Pulmonary surgery	Thoracic wall corr.
IM group	10	6	4	45 (18)	8	2
EPID group	14	12	2	29 (20)	5	9

For postoperative analgesia nicomorphine was used by either the i.m. or the epidural route (Vilan®, Nourypharma, Oss, the Netherlands, preservative-free). The anaesthetic management in both groups of

patients was identical to exclude effects on ventilation of different drugs. The study design eliminated also influences of premedication and of intraoperative medication, to ensure pure effects of nicomorphine on ventilation. Pain relief was assessed by using the VAS.

Methods

For measurement of the chemosensitive response of ventilation to carbon dioxide the steady state technique was used. Figure 11.1 shows a schematic representation of the breathing system used. The flow resistance of this system is 1.2 cm $H_2O.\ell^{-1}$sec.

Measurements taken in each patient are: minute ventilation ($\dot{V}_E$, $\ell.min^{-1}$) respiration rate (RR, min^{-1}), end-tidal PCO_2 ($P_{ET}CO_2$, kPa) and mouth occlusion pressure at 100 msec after start of inspiration ($P_{0.1}$, cm H_2O). Measurements before and after the operation were performed with the patient in the same position; for patients undergoing a thoracotomy in semi-recumbent position, for patients undergoing thoracic wall corrections in supine position. Patients undergoing thoracic wall corrections had to stay in the supine position during four days for surgical reasons. For this reason measurements before the operation were performed in the same position. It was also carefully checked that there was no intake of food, drugs, tea, coffee or alcohol within two hours before measurements. A response due to oxygen, in patients for whom a substantial oxygen drive might be present, was avoided by choice of CO_2 in air, not enriched with oxygen.

Of four consecutive steady state measurements of $\dot{V}_E$, RR, $P_{0.1}$ and $P_{ET}CO_2$ average values were calculated. At first, measurements were made with the patient breathing room air (F_iO_2 = 20.9%, F_iCO_2 = 0). Immediately thereafter the same procedure was followed, the patient now breathing a gas-mixture of 5% CO_2 in air (F_iO_2 = 19.8%), provided by a gas-cylinder in the fresh gas inlet of the system via a reservoir bag. In every patient this procedure was performed three times; firstly the day before operation, secondly the first day after the operation before nicomorphine administation and finally after nicomorphine, at the time $P_{ET}CO_2$ was maximal.

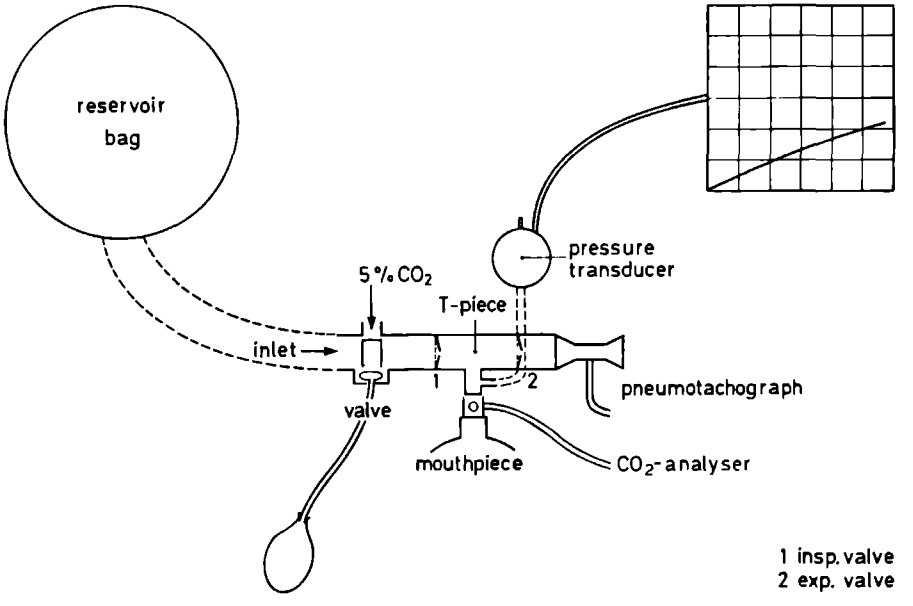

FIG. (11.1) *Schematic representation of the experimental set-up used in this study for measurement of ventilatory response in* $\dot{V}_E$ *and* $P_{0.1}$ *to* CO_2. $\dot{V}_E$ *is measured by an integrating pneumotachograph in the expiratory limb of a standard combination of T-piece and mouth-piece. The inspiratory limb is connected to either room air, or to a reservoir bag filled with* CO_2*-enriched air. A* CO_2*-analyser as well as a pressure transducer are directly coupled to the mouth-piece. The mouth occlusion valve is manually operated by a balloon.*

Measurement procedure.

After an explanation of the experimental procedure the patient was connected to the system and a nose clip was put on. Measurements

with room air started after two minutes when breathing through the system had been stabilized. The minute ventilation was measured by integrating the flow (Calculair Hospal flow meter) in the expiratory limb of the system over a period of one minute. In this very minute $P_{ET}CO_2$ was displayed and recorded continuously measured by infra-red absorption with a Siemens Sirecust 404 capnograph. The latter instrument also continuously displayed respiratory rate.

After measuring minute ventilation, $P_{ET}CO_2$ and RR during one minute, $P_{0.1}$ was measured by occluding the inspiratory limb of the system by manual inflation of a rubber balloon during an expiratory-phase of the patient, such that occlusion did not disturb his breathing. Occlusion could not be detected by the patient in any way to exclude anticipation. The effort of the patient for the following inspiration was measured as a negative pressure in the T-piece of the system. Immediately after completing the measurement of $P_{0.1}$ the valve was reopened to return to normal inspiration. The pressure developed was sensed by a pressure transducer (Model PT5 volumetric pressure transducer, Grass Instruments) connected to the T-piece of the system. A storage oscilloscope (Tektronix 7623 A), also connected to the pressure transducer registered the pressure-time curve in the first 100 msec. of inspiration on its screen. The screen was photographed. Calibration of the pressure measurement was performed with the aid of a water-manometer before each measurement.

When four measurements were completed with the patient breathing room air, the system was extended with a reservoir bag and a wide-bore inspiratory limb, both connected to the inlet of the T-piece. A gas-cylinder containing 5% CO_2 in air was also connected to this side of the T-piece. Before reconnecting the patient to the breathing system, it was completely washed and filled with this gas-mixture. Then the patient was reconnected to the system. Measurements were made after a steady-state level of $P_{ET}CO_2$ had been reached, as observed on the display of the capnograph. Again four consecutive measurements of $\dot{V}_E$, $P_{ET}CO_2$, RR and $P_{0.1}$ were made.

The first day after surgery this whole procedure was repeated at the moment the patient requested analgesic treatment, before nicomorphine was administered When measurements were completed analgesic therapy, either i m (0 1 mg kg^{-1}) or epidural nicomorphine (5 mg in 10 ml dextrose 5%) was given Directly after nicomorphine administration $P_{ET}CO_2$ was measured at 5 minutes intervals using a face-mask and the infra-red CO_2-analyser of the capnograph to detect the maximum $P_{ET}CO_2$ When the maximum was reached, the whole procedure of measurements was repeated After completing the last series of measurements $P_{ET}CO_2$ measuements were continued at ten-minute intervals to detect a possible secundary rise in $P_{ET}CO_2$

Statistical analysis

Statistical calculations were carried out using the SPSS routine package (SPSS Inc, Chicago Illinois) In relation to the structure of the data, Student's t-test for paired or unpaired data was used In all cases $p < 0\ 05$ was considered significant.

11 3 Results

Results on the ventilatory responses to CO_2 are listed in table 2. In this table all changes in V_E, $P_{ET}CO_2$, RR and $P_{0\ 1}$ due to CO_2 stimulation proved statistical significant. There are no significant differences between preoperative values between the IM and EPID groups The same holds for values measured postoperatively before administration of nicomorphine There is a significant change in the slope $\Delta V_E/\Delta P_{ET}CO_2$ in the IM group after administation of nicomorphine ($p = 0.03$). The slope $\Delta P_{0.1}/\Delta P_{ET}CO_2$ did not significantly change ($p = 0\ 37$) In the EPID group no significant changes in either slope have been observed.

Table 3 shows the mean apnoeic threshold-$P_{ET}CO_2$ for both the IM- and the EPID- groups. The apnoeic threshold $P_{ET}CO_2$ is defined as the intersection of the extrapolation of the CO_2-response line with the $P_{ET}CO_2$-axis

Table 2

Measurements and results of the ventilatory response to carbon dioxide, in the IM and the EPID group. Average values of 10 patients in the IM and 14 patients in the EPID group with standard deviations in parentheses. Some significances of differences (p values) for paired data are listed at the bottom two lines for each group. Note that "$\Delta P_{0.1}/\Delta P_{ET}CO_2$" can be expressed as a dimensionless number. For sake of comparibility with other literature $P_{0.1}$ is expressed in cm H_2O, resulting in (cm H_2O kPa^{-1}) as a unit of "$\Delta P_{0.1}/\Delta P_{ET}CO_2$"

IM-group (N=10)

	Pre-operative		Postoperative: Before Nicomorphin		Postoperative: After Nicomorphin	
	air	5% CO_2	air	5% CO_2	air	5% CO_2
V_E (ℓ min^{-1})	8.3(1.8)	17.7(3.8)	6.8(2.0)	17.0(8.3)	6.3(1.6)	13.4(5.4)
$P_{ET}CO_2$ (kPa)	5.0(0.4)	6.5(0.3)	5.0(0.7)	6.8(0.4)	5.0(0.9)	6.9(0.6)
RR (min^{-1})	17.4(3.5)	20.1(3.1)	20.7(3.1)	26.6(3.2)	19.3(3.4)	22.7(2.9)
$P_{0.1}$ (cm H_2O)	0.9(0.3)	3.9(1.4)	1.5(0.7)	4.1(2.3)	1.4(0.6)	3.7(2.1)
$\Delta V_E/\Delta P_{ET}CO_2$ (ℓ $min^{-1}kPa^{-1}$)	7.1(4.3)		5.7(3.5)	(p=0.03)	4.0(2.3)	
$\Delta P_{0.1}/\Delta P_{ET}CO_2$ (cm H_2O kPa^{-1})	1.3(0.8)		1.6(1.0)	(p=0.37)	1.4(1.0)	

EPI-group (N=14)

	Pre-operative		Postoperative: Before Nicomorphin		Postoperative: After Nicomorphin	
	air	5% CO_2	air	5% CO_2	air	5% CO_2
V_E (ℓ min^{-1})	9.7(3.1)	23.3(10)	8.1(2.3)	19.2(13)	6.8(2.2)	14.2(6.2)
$P_{ET}CO_2$ (kPa)	4.8(0.6)	6.5(0.4)	5.1(0.7)	7.1(0.6)	5.2(0.7)	7.2(0.7)
RR (min^{-1})	20.5(6.2)	21.2(4.7)	26.8(6.6)	32.6(10)	23.1(6.0)	29.0(9.2)
$P_{0.1}$ (cm H_2O)	1.6(0.7)	3.8(1.4)	1.7(0.7)	4.4(1.6)	1.4(0.5)	3.7(1.3)
$\Delta V_E/\Delta P_{ET}CO_2$ (ℓ $min^{-1}kPa^{-1}$)	9.6(7.0)		6.2(4.9)	(p=0.16)	4.2(3.1)	
$\Delta P_{0.1}/\Delta P_{ET}CO_2$ (cm H_2O kPa^{-1})	1.6(1.0)		1.8(1.2)	(p=0.12)	1.3(0.8)	

Table 3: Apnoeic threshold-$P_{ET}CO_2$-values.

Effect of epidural and i.m. nicomorphine on the mean apnoeic threshold assessed by $\dot{V}_E$ and by $P_{0.1}$.

1. preoperative value
2. postoperative value before nicomorphine
3. postoperative value after nicomorphine

time measurement	1	2	3
group			
I.M. group			
calc from $\dot{V}_E$	3.1(1.8)	3.5(1.1)	2.3(3.8)
calc from $P_{0.1}$	3.7(1.5)	4.0(1.0)	2.5(4.2)
EPID group			
calc from $\dot{V}_E$	2.8(2.7)	2.8(2.3)	2.8(1.9)
calc from $P_{0.1}$	4.6(4.5)	3.7(1.5)	3.3(2.0)

After administering nicomorphine the mean apnoeic threshold is not significantly shifted in either group.

In figures 11.2 and 11.3 the individual ventilatory responses to CO_2 in both groups are shown.
Note the large inter-individual variation in ventilatory response to CO_2, especially before the operation. Some patients are not depicted in figures 11.2 and 11.3, because of missing data pre- or postoperatively.

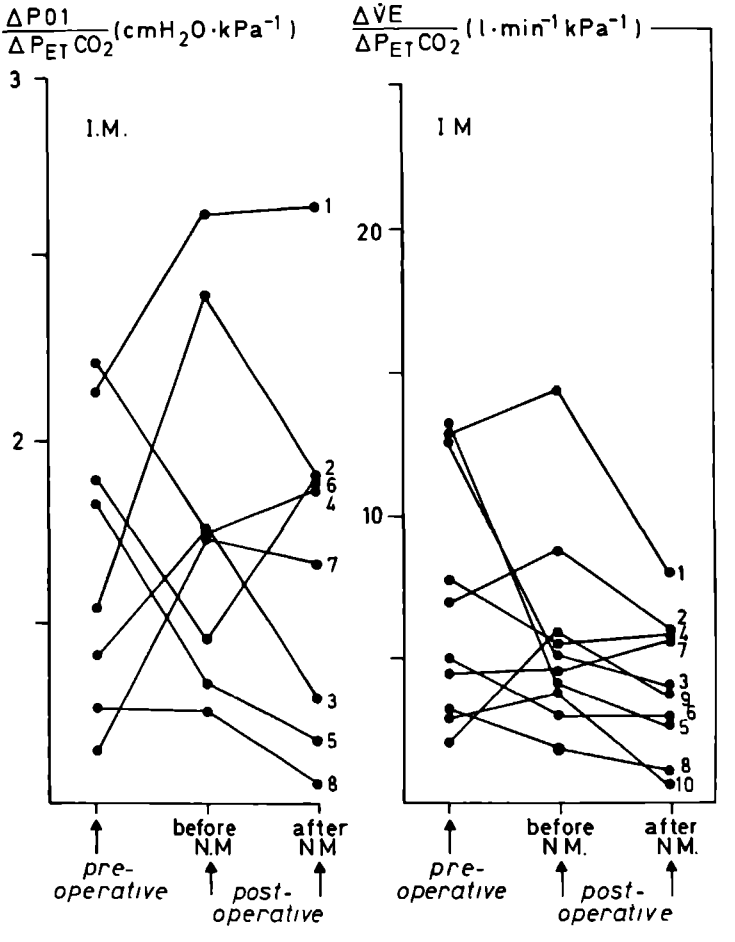

FIG. (11.2) *Individual ventilatory response to CO_2 in the IM group. Changes in $\Delta\dot{V}_E/\Delta P_{ET}CO_2$ in 10 patients and $\Delta P_{0.1}/\Delta P_{ET}CO_2$ in 8 patients are shown at three different times (preoperatively, postoperatively before and after nicomorphine). Each numbered "line" represents an individual patient.*

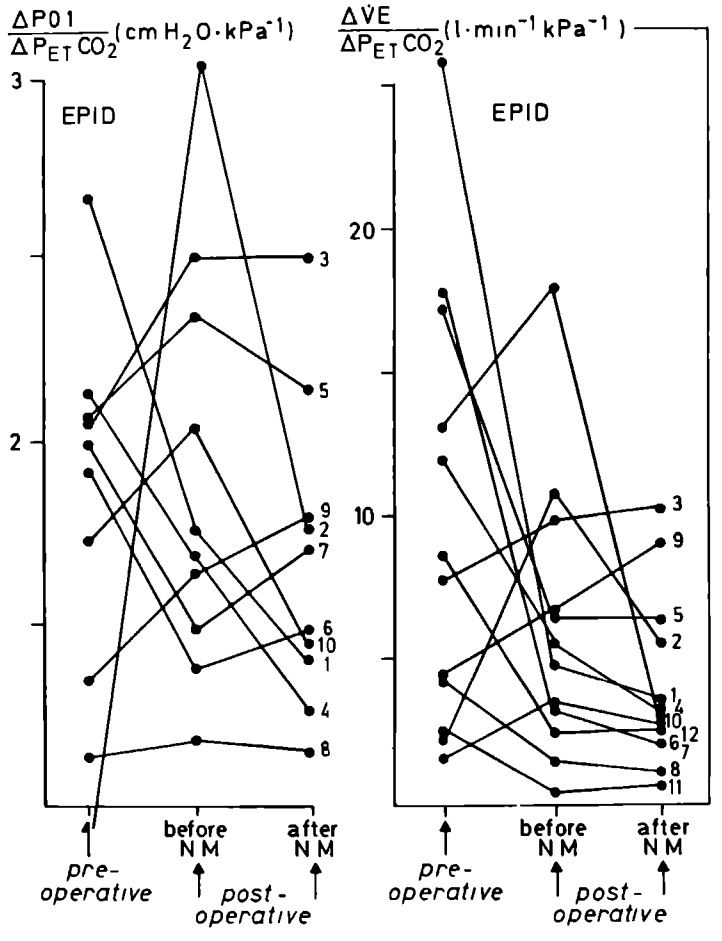

FIG. (11.3) *Individual ventilatory response to CO_2 in the EPID group. Changes in $\Delta\dot{V}_E/\Delta P_{ET}CO_2$ in 12 patients and $\Delta P_{0.1}/\Delta P_{ET}CO_2$ in 10 patients are shown at three different times (see also legend of figure 11.2).*

11.4 Discussion

Nicomorphine is the 3,6-dinicotinoyl ester of morphine. It probably acts as a pro-drug, and is reported to be equipotent compared to morphine (Nielsen, 1984). Up till now no clinical reports of ventilatory depression following (epidural) administration of nicomorphine have been published. This is in contrast to several reports of prolonged ventilatory depressive effects after subarachnoid and epidural morphine and diamorphine (Doblar, 1982; Gustafsson, 1982; McCaughey, 1982; Kafer, 1983; Malins, 1984). Even with the epidural catheter inserted at T3-T4 level no signs of ventilatory depression were found (Chapter 7). To provide for some additional proof of this, we investigated nicomorphine in similar patient groups as in our earlier study (Chapter 7).

In spite of its time consuming aspect, the steady-state method was chosen arbitrarely instead of the rebreathing technique, to assess the effect of inhaled carbon dioxide on ventilation (Dempsey, 1976; Jordan, 1982). Theoretically, in a patient population where mechanical properties of the lung and chest-wall as well as airway resistance may be affected, the mouth occlusion pressure response to carbon dioxide, should be a more suitable method. The results of this method are not affected by resistance, nor by changes in compliance of the respiratory system (Whitelaw, 1975; Cherniak, 1976; Fitzgerald, 1976).

By performing the measurements not on the the day of surgery, but the first day after, influences of premedication, intraoperative inhalation or intravenous agents on the respiratory response to CO_2 were avoided. Pain was not a complicating factor in the interpretation of the data since both patient groups responded comparably in their VAS pain scores. Pain relief in both groups was adequate. (VAS scores before administration of nicomorphine were 5.8(sd=1.4) in the IM-group and 6.3(sd=2.4) in the EPID-group. At the time of maximal pain relief these scores were 2.3(sd=1.0) and 1.7(sd=0.8) respectively.) After completion of the protocolled measurements monitoring was continued by measuring $P_{ET}CO_2$ at

10 minutes intervals. By this method the possibility of a biphasic depression of the ventilatory response, as previously observed with morphine (Kafer, 1983), was excluded.

Preoperatively, there was a considerable variability in the ventilatory response to CO_2, most probably due to anxiety or airway resistance in various patients. This anxiety is also reflected in the high respiratory rate preoperatively. In figure 11.3 patient 2 shows an extraordinary preoperative point as assessed by $\Delta P_{0.1}/\Delta P_{ET}CO_2$. This also can be explained by the extreme hyperventilation in the first measurements with room air due to anxiety.

The difference in mean age between the IM group and the EPID group is explained by some young patients undergoing corrections of the thoracic wall. This difference in age does not obscure the results in favor of the EPID group, since younger patients proved to have diminished ventilation compared to older patients undergoing thoracic pulmonary surgery (Chapters 7 and 8). Though the absolute drop of $\Delta\dot{V}_E/\Delta P_{ET}CO_2$ due to nicomorphine is comparable in the two groups, the effect is significant in the IM group because of the smaller standard deviations compared to those in the EPID group. Depressant drugs are known to shift $\dot{V}_E$ as a function of PCO_2 to the right. As shown in table 3 this does not occur with nicomorphine.

Nicomorphine influences ventilation maximally between 30 and 45 minutes when given by either route as seen in the rise of $P_{ET}CO_2$. This depression may be due to absorbtion in the venous plexus (Chauvin, 1981), but more probably, since the tip of the catheter was placed at an average T2 level, due to transfer of nicomorphine by the spinal fluid (CSF), moving upwards to the respiratory center. The difference in depressive effect of nicomorphine and morphine, may be related to the lipophilic character of nicomorphine in contrast to morphine, being more hydrophilic. A more hydrophylic opiate is expected to linger more easily in the water phase of the CSF.

Another specific effect of nicomorphine is that cholinergic mechanisms may play a role in its actions on spinal level, the importance of which relates to data which indicated the reduction of the respiratory depressant actions by opiates in the presence of an increased cholinergic tone (Dirksen, 1984). In spite of some steep individual decrease in the CO_2 response after nicomorphine administration (figures 11.2 and 11.3) the corresponding $PaCO_2$ at that particular moment never exceeded 7.9 kPa. The $PaCO_2$ values of all patients remained in the range of 5.2 to 7.9 kPa after nicomorphine, being between 4.0 and 6.2 kPa preoperatively.

In conclusion, in contrast to reports on morphine and diamorphine we could not demonstrate a significant difference in CO_2 response between epidural and intramuscular group. Nicomorphine, diluted in dextrose 5%, injected epidurally postoperatively has been found to provide effective analgesia with a rapid onset without producing ventilatory depression (Pinckaers, 1981; Dirksen, 1984) in various thoracic operations despite of high position of the epidural catheter (Chapter 7 and 8). Nicomorphine, administered epidurally, therefore proves an effective, safe and by experience feasible postoperative analgesic.

11.5 References

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Chapter 1. The first chapter points out that thoracotomy is a very painful operation, with a great need for postoperative analgesia. Patients undergoing thoracic surgery are often of advanced age, heavy smokers, have cardiovascular disturbances and sometimes with chronic obstructive pulmonary disease. These factors increase the risk of postoperative pulmonary complications.

The aim of the study was to reduce the number of these postoperative pulmonary complications.

For this reason four patient groups had been selected with different analgesia during and after operation in every group, to choose the best combination of analgesia during and after operation with respect to the prevention of postoperative pulmonary complications.

Chapter 2. This chapter discusses the most important anatomical characteristics with regard to the thoracic approach of the epidural space. At the thoracic level the spinal cord is present, which whenever damaged may be a disasterous complication for the patient. In the mid-thoracic region (T4-T8) there is a steep angulation and overlap of the spinous processes and laminae. At this level only the paramedian epidural approach is possible. Above the fourth and below the eighth thoracic vertebra the angulation becomes less, and both median and paramedian approach of the epidural space are possible.

Chapter 3. Epidural analgesia with local anaesthetics affects various organ systems. From these systems the influence of epidural analgesia on the cardiovascular and respiratory system, are discussed. Theoretically upper thoracic epidural analgesia reduces cardiac performance, depending on the local anaesthetic used. On the respiratory system a reduction of afferent input by the epidural

blockade has definite advantages with respect to the ventilation, which are pointed out in this chapter.

Chapter 4. In this chapter the technique of inserting an epidural catheter at thoracic level is explained and discussed, with special reference to the hanging drop technique and the paramedian approach to the thoracic epidural space.

Chapter 5. In this chapter, two possible complications of thoracic epidural analgesia are briefly discussed, spinal cord damamge and late respiratory depression. The attention is focussed on the complication most feared: late respiratory depression. In the literature late respiratory depression mostly occurs with hydrophilic opiates, such as morphine, but has not yet been reported by lipophilic opiates such as nicomorphine.

Chapter 6. This chapter describes the most frequently occurring complication after thoracic surgery: atelectasis. There is a discussion as to why the reported incidence of atelectasis after thoracic surgery varies considerably in the various studies. The predictability of postoperative pulmonary complications and how to prevent them with emphasis on the analgesia, are summarized. The various methods of pain relief after thoracic surgery are briefly discussed. Three relatively new techniques of pain relief after thoracic surgery are mentioned.

Chapter 7. One hundred sixty-three patients subjected to three different types of thoracic operations, were allocated randomly either for balanced intravenous anaesthesia including i.v. opiates with postoperative intramuscular opiates (intramuscular group) or for balanced intravenous anaesthesia without i.v. opiates but with high thoracic epidural regional block during the operation as well as epidural nicomorphine postoperatively (epidural group).

Postoperative nicomorphine was given only at the request of the patient and as frequently as needed to obtain satisfactory pain relief Patients in the epidural group received nicomorphine exclusively by epidural injection In this paper (part I) general parameters between the epidural group and the i m group are compared

The epidural group showed acceptable cardiovascular stability during the operation With the catheter tip at the T3-T4 level there was apparently a preferential spread downwards of the local anaesthetics Postoperatively both groups (i.m and epidural) provided effective and rapid onset of analgesia There were no major differences in postoperative pain assessment, neither by the patient, nor by the team

Chapter 8. One hundred and sixty-three patients subjected to three different types of thoracic operations, were allocated randomly either for balanced intravenous anaesthesia including i.v.opiates with postoperative intramuscular opiates (intramuscular group) or for balanced intravenous anaesthesia without i.v. opiates but with high thoracic epidural regional block during the operation as well as epidural nicomorphine postoperatively (epidural group) Postoperative nicomorphine in either group was given only at the request of the patient and as frequently as needed to obtain satisfactory pain relief. Patients in the epidural group were given nicomorphine exclusively by epidural injection

Patients in the epidural group required significantly less nicomorphine for effective pain relief (29 mg(sd=10) over a period of 3 days compared to the intramuscular group 52 mg(sd=27)) Significantly fewer pulmonary complications in the epidural group were observed (9 atelectases in 83 patients in the epidural group compared to 23 atelectases in 80 patients in the intramuscular group). Only one patient developed a pneumonia (intramuscular group) Although the epidural catheter was inserted at T3-T4 level no signs of ventilatory depression were found; on the contrary, the epidural group ventilated significantly better than the intramuscular group None of the patients, in either analgesia

group, needed to be ventilated postoperatively.

Chapter 9. One hundred and twenty-nine patients subjected to three different types of thoracic operations were allocated randomly either to balanced intravenous anaesthesia including i.v. nicomorphine with postoperative epidural nicomorphine (epidural group, n=58) or to balanced intravenous anaesthesia without i.v. opiates but with high thoracic epidural regional block during the operation with postoperative intramuscular nicomorphine (intramuscular group, n=71). Postoperative nicomorphine was only given at the request of the patients and as frequently as needed to obtain satisfactory pain relief. Patients in the epidural group were given nicomorphine exclusively by epidural injection. Postoperatively both groups (i.m. and epidural) provided effective and rapid onset of analgesia, but the pain assessment by the patient and the medical team were in favour of the epidural group. In the epidural group the requirements of nicomorphine over a period of 3 days were significantly lower, 42 mg (sd=18) versus 92 mg (sd=33) in the intramuscular group. Significantly fewer pulmonary complications were observed in the epidural group, 7 atelectases compared to 27 in the intramuscular group. The epidural group showed no signs of ventilatory depression in spite of a catheter inserted at the T3-T4 level. In the discussion a comparison between the intramuscular and epidural group of the previous parts (I and II) with the groups of this part (III) is made. No correlation with pulmonary function tests before surgery and pulmonary complications (after surgery) was found.

Chapter 10. The effect of high thoracic epidural analgesia (TEA) on the cardiovascular system was investigated in 10 patients (5 with cardiovascular disease and 5 without any cardiovascular disorder), who were scheduled for a thoracotomy. An epidural catheter was inserted at T1-T2 level. Plain bupivacaine (Marcaine®) 0.5%, 4 to 6 ml was used and resulted in a mean analgesic level from C7 to T5.

TEA did not significantly affect the following parameters: heart

rate, mean arterial pressure, cardiac index, central venous pressure, pulmonary capillary wedge pressure, stroke volume index, systemic vascular resistance, pulmonary vascular resistance, right and left ventricular stroke work index. Even in 3 patients using β-adrenoceptor antagonists, of whom 1 patient had myocardial infarction previously, TEA did not affect these parameters

From this study it is concluded that high TEA with bupivacaine has only minor effects on the cardiovascular system

Chapter 11 In this study the effects of nicomorphine, administered either intramuscularly or high thoracic epidurally, on the ventilatory and airway occlusion pressure response to CO_2 were investigated and compared Twenty-four patients scheduled for thoracic surgery were allocated randomly for postoperative pain relief by i m nicomorphine or by high thoracic epidural nicomorphine

Ventilatory response to 5% carbon dioxide was measured in all patients firstly one day before operation, secondly the first day after surgery immediately before nicomorphine administration and finally after the administration, at the moment that no further rise in end-tidal P_{CO_2} ($P_{ET}CO_2$)was measured Respiratory response was assessed in two ways, by measuring minute ventilation (V_E) and mouth occlusion pressure ($P_{0.1}$)

There was a significant depression in ventilatory response to CO_2 in the intramuscular group ($p = 0.03$) due to nicomorphine as assessed by the slope of V_E vs $P_{ET}CO_2$. No significant depression was found in the epidural group, irrespective of measurement of $\dot{V}_E$ or $P_{0.1}$ No significant shift of apnoeic threshold-$P_{ET}CO_2$ was observed in either group

Conclusions

1. The placement of a high-thoracic epidural catheter, as well as the administration of the local anaesthetic bupivacaine 0.5% with adrenaline 1:200,000 at thoracic level, is a safe anaesthetic technique.

2. Pain relief after thoracic surgery by the high-thoracic administration of nicomorphine is superior to the intramuscular administration of nicomorphine.

3. By the postoperative administration of high-thoracic epidural nicomorphine one can reduce the number of postoperative pulmonary complications after thoracic surgery.

4. By the peroperative administration of the local anaesthetic bupivacaine 0.5% with adrenaline 1:200,000 during thoracic surgery, the postoperative epidural requirements for nicomorphine are reduced.

5. Postoperative ventilation after thoracic surgery is better after the peroperative use of the local anaesthetic bupivacaine 0.5% with adrenaline 1:200,000 than after the intravenous administration of nicomorphine.

6. High-thoracic epidural administration of nicomorphine depresses ventilation only slightly, but in comparison to intramuscular administration of nicomorphine after thoracic surgery ventilation is found to be better with epidural administration.

Hoofdstuk 1. Een thoracotomie is een zeer pijnlijke operatie, met een grote behoefte aan postoperatieve pijnbestrijding. Patiënten, die thoraxoperaties ondergaan, zijn veelal oudere patiënten, rokers, met cardiovasculaire afwijkingen en longfunctiestoornissen. Deze factoren dragen bij tot de grotere kans op het ontwikkelen van postoperatieve longcomplicaties. Het doel van deze studie is na te gaan of het aantal hiervan is te verminderen. Om dit doel te bereiken werden 4 analgesie-technieken vergeleken met elkaar om op deze manier de beste pijnbestrijding te vinden en zo het aantal postoperatieve longcomplicaties te verminderen.

Hoofdstuk 2. In dit hoofdstuk worden de belangrijkste anatomische karakteristieken met betrekking tot de thoracale benadering van de epidurale ruimte besproken. Op thoracaal niveau is de epidurale ruimte smal en kan met de epidurale naald het ruggemerg worden beschadigd. Ter hoogte van de thoracale wervels 4 tot en met 8 lopen de doornuitsteeksels zo schuin, dat vrijwel alleen via een paramediane benadering de epidurale ruimte bereikbaar is. Boven de vierde en beneden de achtste thoracale wervel lopen de doornuitsteeksels geleidelijk minder schuin, en is zowel de mediane als de paramediane benadering van de epidurale ruimte mogelijk.

Hoofdstuk 3. Epidurale analgesie door middel van locaalanaesthetica beïnvloedt de functie van meerdere orgaan systemen. Alleen de invloed op het hart en de ademhaling wordt hier besproken. Gezien de innervatie van het hart vanuit de bovenste vier thoracale segmenten van het ruggemerg, kan men na epidurale analgesie een verandering van de circulatie verwachten, die afhankelijk is van de dosis en het soort locaalanaestheticum. Een vermindering van de afferente signalen door middel van epidurale analgesie, heeft, met betrekking tot de ademhaling, bepaalde voordelen die in dit hoofdstuk worden uiteengezet.

Hoofdstuk 4. In dit hoofdstuk wordt een veilige techniek besproken om een epidurale catheter in de thoracale epidurale ruimte te plaatsen. Dit is de "hanging drop techniek" via de paramediane benadering.

Hoofdstuk 5. In dit hoofdstuk worden twee mogelijke complicaties van thoracale epidurale analgesie besproken, namelijk de beschadiging van het ruggemerg met de epidurale naald en de ademdepressie door epidurale toediening van opiaten. De aandacht richt zich in het bijzonder op de ademdepressie. Deze wordt in de literatuur vooral beschreven na de toediening van goed in water oplosbare analgetica zoals morfine. Bij de beter in vet oplosbare analgetica zoals nicomorfine wordt deze ademdepressie niet gezien. De mogelijke theoretische achtergronden van de verschillende farmacokinetische werkingen tussen morfine en nicomorfine worden uiteengezet.

Hoofdstuk 6. De meest frequente complicatie na thoraxchirurgie is de atelectase. De incidentie hiervan varieert in de diverse studies en dit verschil in incidentie is van diverse factoren afhankelijk. In dit hoofdstuk wordt verder uiteengezet of postoperatieve longcomplicaties voorspelbaar zijn en hoe deze complicaties te voorkomen zijn.
Speciale aandacht in dit verband wordt besteed aan de diverse methodieken van pijnbestrijding na thoraxoperaties.

Hoofdstuk 7. In dit hoofdstuk worden 163 patiënten besproken. Het betreft een prospectief gerandomiseerd onderzoek met drie verschillende types thoraxoperaties. Deze patiënten werden ingedeeld voor wat betreft de pijnbestrijding in 2 groepen: de eerste groep kreeg gedurende de operatie nicomorfine intraveneus en na de operatie intramusculair toegediend (IM groep, n=80); de tweede groep kreeg gedurende de operatie pijnbestrijding door middel van een locaalanaestheticum, hoog-thoracaal epiduraal toegediend, en na

de operatie werd de pijnbestrijding, eveneens hoog-thoracaal epiduraal, via nicomorfine bewerkstelligd (EPID groep, n=83).

De patiënten kregen na de operatie bij pijn, op verzoek nicomorfine, zoveel als nodig was om voldoende analgesie te verkrijgen. In de EPID groep werd de nicomorfine alleen per epidurale catheter toegediend. Bij beide groepen werden vergeleken: de demografische gegevens en de postoperatieve pijn (evaluatie vond plaats door een medisch team en door de patiënt zelf). Eveneens werden de complicaties van de gebruikte hoog thoracale epidurale techniek geëvalueerd, evenals de techniek zelf.

Uit de demografische gegevens bleek de EPID groep meer C.A.R.A. patiënten te bevatten, meer patiënten met overgewicht te hebben en de patiënten in de epidurale groep bleken ouder te zijn. De analgesie in de IM en de EPID groep bleek even effectief en snel te zijn, en de evaluatie van de pijn door het medisch team en de patiënt bleek ook gelijk. Deze pijnevaluatie vond plaats 3 dagen na de operatie. Omdat deze evaluatie later in het protocol was ingevoerd, is statistische bewerking achterwege gelaten.

Als controle op de juiste localisatie van de naald in de epidurale ruimte werd de "hanging drop" test toegepast, die in 97% van de gevallen positief bleek. Slechts éénmaal werd de dura geperforeerd en in geen van de gevallen werd een locaalanaestheticum in een epiduraal bloedvat gespoten. Met het gebruik van het locaalanaestheticum bupivacaine 0.5% met adrenaline 1:200.000, was slechts in 6% van de gevallen een bloedvat vernauwend farmacon noodzakelijk om een bloeddrukdaling op te vangen.

Hoofdstuk 8. In de analgesie groepen zoals deze in hoofdstuk 7 zijn beschreven, werden de volgende gegevens bestudeerd: de behoefte aan nicomorfine, de pre- en postoperatieve arteriële koolzuurspanning, de postoperatieve complicaties (atelectasen en het aantal afzuigbronchoscopieën), de complicaties ten gevolge van het gebruik van opiaten en de incidentie van postoperatieve hartritmestoornissen.

De behoefte aan nicomorfine was gedurende de eerste drie dagen in de EPID groep minder [29 mg (sd=10)] dan in de IM groep [52 mg

(sd=27)]. De ventilatie in de EPID groep was gedurende deze zelfde periode beter ondanks analgesie via een hoog-thoracale epidurale catheter. Het aantal complicaties was in de EPID groep (9 atelectases in 83 patiënten), significant lager dan in de IM groep (23 atelectases in 80 patiënten). In de EPID groep werd significant meer urine retentie vastgesteld, echter ook significant minder sufheid. Het aantal hartritmestoornissen was niet significant verschillend in beide groepen.

Hoofdstuk 9. De beide analgesie groepen zoals deze in de hoofdstukken 7 en 8 zijn beschreven, kregen zowel per- als postoperatief verschillende analgetica op verschillende wijze. De betere postoperatieve resultaten in de EPID groep patiënten zouden zowel het gevolg kunnen zijn van de bupivacaine 0.5% met adrenaline 1:200.000 tijdens de operatie, maar ook ten gevolge van de epidurale toediening van nicomorfine postoperatief of aan de combinatie van beide. Om dit te onderzoeken werden complementaire analgesie groepen bestudeerd (n=128), terwijl de anaesthesie techniek hetzelfde bleef als in de hoofdstukken 7 en 8.

Nu bleek geen verschil in demografische gegevens tussen beide complementaire analgesie groepen. Significant betere resultaten in de EPID groep (n=58) dan in de IM groep (n=71) werden verkregen niet alleen met betrekking tot de postoperatieve pijn evaluatie, maar ook tot het nicomorfine gebruik gedurende 3 dagen [42 mg (sd=18) tegenover 92 mg (sd=33)], terwijl het aantal atelectases 7 bedroeg in de EPID groep tegenover 27 in de IM groep. Ook nu was er geen sprake van een ademhalingsdepressie in de EPID groep ondanks de hoog-thoracale epidurale catheter en er deden zich geen complicaties voor door de hoog-thoracale epidurale techniek. Ook in deze EPID groep waren de patiënten significant minder suf na het bijspuiten van de epidurale catheter dan na de toediening van nicomorfine intramusculair. Er waren geen significante verschillen in de frequenties waarmee urineretentie of hartritmestoornissen in deze beide analgesie groepen optraden. In de totale studie (hoofdstukken 7, 8 en 9) werd geen significant verschil gezien in de preoperatieve longfunctietesten (gerelateerd aan de individuele normaal waarden)

tussen patiënten *met* en *zonder* postoperatieve atelectase.

Hoofdstuk 10. Het effect van hoog-thoracale epidurale analgesie (T.E.A.) op het cardiovasculaire systeem werd onderzocht in 10 patiënten (5 *met*, en 5 *zonder* cardiovasculaire afwijkingen). De epidurale catheter werd ingebracht op het niveau van de thoracale wervels 1-2. Als locaalanaestheticum werd bupivacaine 0.5% (Marcaine®) 4-6 ml gebruikt, en het analgesie niveau lag tussen de dermatomen van cervicale 7 en thoracale 5. Door middel van een Swan-Ganz thermodilutie catheter werd vastgesteld dat bupivacaine 0.5% slechts geringe invloed heeft op de prestaties van het hart.

Hoofdstuk 11. In deze studie, bestaande uit 24 patiënten werden de effecten van intramusculair versus hoog-thoracaal epiduraal toegediende nicomorfine bestudeerd en vergeleken, zowel op ventilatie als op "airway occlusion pressure" ($P_{0.1}$, de drukdaling in de mond gedurende de eerste 100 milliseconden van de inademing bij een afgesloten luchtweg). Deze effecten werden gemeten voor en na stimulatie door middel van 5% CO_2. De ventilatoire reactie werd bij alle patiënten gemeten een dag voor de operatie, een dag na de operatie, en wel voor en na de toediening van nicomorfine. Na de toediening van de nicomorfine werden op het moment dat de eind-expiratoire PCO_2 een plateau had bereikt de metingen verricht. De ventilatoire reactie werd bestudeerd op twee manieren, door meting van het ademminutenvolume ($\dot{V}_E$) en door meting van de $P_{0.1}$. De ventilatoire reactie op CO_2 stimulatie daalde significant in de intramusculaire groep ($p=0.03$), gemeten via het ademminutenvolume. In de epidurale groep werd geen significante verandering gezien in de ventilatoire reactie. Bij iedere patiënt werd het snijpunt berekend met de x-as ($P_{ET}CO_2$) van de rechte, die werd verkregen door de twee meetpunten voor $\dot{V}_E$ of $P_{0.1}$ voor en na toediening van 5% CO_2 te verbinden. Het afgesneden stuk van de x-as ("apnoeic threshold", de drempel P_{CO_2}-waarde waarbij de patiënt theoretisch ophoudt met ademen), veranderde gemiddeld voor de patiënten (hetzij IM of EPID) niet van plaats onder invloed van de toegediende nicomorfine.

Conclusies

1. Zowel het plaatsen van een hoog-thoracale epidurale catheter, alsmede de toediening van het locaalanaestheticum bupivacaine 0.5% met adrenaline 1 : 200.000 op thoracaal niveau is een veilige anaesthesie-techniek.

2. Pijnbestrijding na thoraxoperaties door middel van de hoog-thoracale epidurale toediening van nicomorfine blijkt effectiever dan door intramusculaire toediening van nicomorfine.

3. Door de postoperatieve hoog-thoracale epidurale toediening van nicomorphine bij thoraxoperaties, is het mogelijk om het aantal postoperatieve longcomplicaties te verminderen.

4. Door de toediening van het locaalanaestheticum bupivacaine 0.5% met adrenaline 1 : 200.000 tijdens thoraxoperaties, kan men de postoperatieve epidurale behoefte aan opiaten verminderen.

5. Met het oog op de postoperatieve ventilatie na thoraxoperaties, verdient de peroperatieve epidurale toediening van het locaalanaestheticum bupivacaine 0.5% met adrenaline 1 : 200.000 de voorkeur boven de peroperatieve intraveneuze toediening van nicomorfine.

6. De hoog-thoracale epidurale toediening van nicomorfine heeft slechts een geringe ademdepressieve werking en indien toegepast na thoraxoperaties wordt een betere ventilatie verkregen dan na intramusculaire toediening.

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Since 1981, he has been a staff member of the same department and a consultant in thoracic anaesthesia.

STELLINGEN

behorende bij het proefschrift

High-Thoracic Epidural Analgesia
During and After Thoracic Surgery

Nijmegen
12 september 1986, 13:30 uur

M.A.W.M. Hasenbos

I

Door een goede analgesie te bewerkstelligen bij thoraxoperaties zowel per- als postoperatief, kunnen een aantal belangrijke postoperatieve pulmonale complicaties worden voorkomen

Dit proefschrift

II

Met het oog op de postoperatieve ventilatie na thoraxoperaties, verdient de peroperatieve epidurale toediening van een locaal anaestheticum de voorkeur boven de peroperatieve intraveneuze toediening van opiaten

Dit proefschrift

III

De hoog-thoracale epidurale toediening van nicomorfine heeft slechts een geringe ademdepressieve werking

Dit proefschrift

IV

De kans dat patienten met C A R A in de 8 weken die volgen op de operatie overlijden ten gevolge van longcomplicaties, is viermaal groter dan het overlijden aan alle andere oorzaken tezamen

Tarhan S e a , Surgery 74 720, 1973

V

Patienten met obstructieve longziekten worden preoperatief meestal niet optimaal voorbehandeld indien op de dag *van* of *voor* de operatie, slechts een infuus met theophylline en corticosteroiden gegeven wordt

VI

Epidurale pijnbestrijding is zowel per- als postoperatief weliswaar in veel gevallen toepasbaar, maar slechts in enkele gevallen noodzakelijk

Bromage P R , Epidural analgesia, 1978

VII

Bij de behandeling van een patient met een multitrauma en een verdenking op ernstige beschadiging van de hersenen (Glasgow Coma Schaal 3,4 of 5), dient men zich te beperken tot de minst tijdrovende manier van fractuur stabilisatie

VIII

Voor de kwaliteit van de patiëntenzorg op de afdelingen van intensieve verpleging in Nederland zou het wenselijk zijn, dat de coördinatie van die zorg in één hand is.

IX

Het al dan niet acuut zijn van een nachtelijke operatie in een academisch ziekenhuis, hangt voor een deel af van de ervaring van de operateur, de nachtrust die hij (zij) nodig meent te hebben en het operatieprogramma van de volgende dag.

X

Als medische specialisten waren uitgerust met slechts dezelfde diagnostische hulpmiddelen als de huisarts, staat het niet vast dat zij betere of zelfs dezelfde resultaten zouden bereiken als de huisarts.

XI

Frequent onderzoek van patiënten en belanghebbenden door huisartsen en specialisten kan leiden tot iatrogene arbeidsongeschiktheid.

XII

Het verschil in inkomen tussen specialisten werkend in academische ziekenhuizen en perifere ziekenhuizen, zegt niets over het "psychisch inkomen" van de academisch werkzame specialist maar wel wat over zijn psyche.

XIII

Uit de wachttijden van patiënten voor polikliniek bezoek in ziekenhuizen, zou men eerder een tekort dan een teveel aan specialisten mogen afleiden.

XIV

Het bezit van een kunstvoorwerp van een bepaalde meester, wil niet zeggen dat dit voorwerp een meesterstuk is.

XV

Doctor werden ist nicht schwer, "Dokter" sein dagegen sehr.

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